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The trends and rates of gabapentin and pregabalin

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The trends and rates of gabapentin and pregabalin

MSc by Research

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Declaration

I hereby declare that I am the author of this thesis, it is a record of the work that has been done by me, and it has not previously been accepted for a higher degree. I also state that all references cited have been consulted by me and the conditions of the relevant ordinance and regulations have been fulfilled.

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Date 03/04/2019

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Abstract

Background

Gabapentinoids were initially introduced for the treatment of epilepsy, then became more widely used in neurology, psychiatry and primary healthcare for the treatment of neuropathic pain. However, gabapentinoids have frequent and debilitating side effects, including viral infection, visual disturbance, nystagmus, fever and fatigue, and recent evidence suggests that they are increasingly misused. What is more, recent studies have found the number of drug-related deaths in which gabapentinoids are implicated is rising. Detailed and published evidence on the prescribing rates and trends of gabapentin and pregabalin is limited. Identifying the prescribing rates and trends of gabapentinoids will help us to quantify the scale of the issue and allow us to examine whether there are associations with demographic factors and subsequent health outcomes.

Objective

This research work consists of two projects. (Part 1) The systematic review, aims to summarise the current published evidence on the trends and rates of gabapentin and pregabalin prescribing among the general population. (Part 2) The data-linkage analysis, aims to summarise the gabapentin and pregabalin prescribing patterns in Tayside over 11 years (2006 to 2016) and Fife over seven years (2010 to 2016). As well as the association of prescribing patterns with sociodemographic factors, the use of related health services was also examined by using routinely available linked data for 2015 and 2016.

Methods

(Part 1) Current published evidence was collected by the following steps: constructing a search strategy for searching selected key databases; selecting papers based on the selection criteria, data abstraction and quality assessment; preparing a table summary for the included papers; and summarizing the included citations.

(Part 2) A large dataset including 1,091,199 prescriptions and data-linkage from data prepared by Health Informatics Centre (HIC) services was analysed. The prescribing patterns of gabapentinoids in Tayside over 11 years (2006 to 2016) and Fife for seven years (2010 to 2016) were summarised and compared with Scottish national data using Excel and SPSS. The 36,800 patients who were prescribed at least one gabapentin or pregabalin in Tayside and Fife during 2015 and 2016 were linked with the demographic file, SMR06 cancer register file, SMR01 hospital admission file, GRO death data, accident and emergency data and SMR00 outpatient file, using routine data obtained from HIC at the University of Dundee. The association of prescribing patterns with socio-demographic factors was examined using both logistic regression modelling and Poisson modelling; while their association with using the health services was investigated by a correlation graph. The age standardised mortality and the underlying cause of death were also calculated and summarised.

Results

(Part 1) 529 non-duplications were retrieved and 17 citations were included following the process of paper selection. The trends of gabapentin and pregabalin prescribing varied from country to country: rise, decrease and fluctuation. The rates of gabapentin

and pregabalin prescribing varied in different countries within the same year. Among the 17 papers, there were five papers of high quality, nine papers of medium quality and three papers of low quality.
(Part 2) The number of gabapentin prescriptions in Scotland rose 4-fold from 164,630 in 2006 to 694,293 in 2016. In Tayside these figures were 16,481 in 2006 to 57,472 in 2016 (x3.5). In Fife, there were 20,465 prescriptions issued in 2010, rising to 65,241 in 2016 (x3.2). Similar rises in the number of pregabalin prescriptions were charted in Scotland (x16.1), Tayside (x21.4) and Fife (x2.4). Health board, age and The Scottish Index of Multiple Deprivation (SIMD) were significantly related to rates of gabapentin and pregabalin prescribing. The age standardised death rate among the population prescribed gabapentinoids was significantly higher than that reported among the Scottish general population ($p<0.001$).

Conclusion

(Part 1) The systematic review found that trends of gabapentin and pregabalin prescribing varied in different countries. Because of the limitations of these papers, a further and more comprehensive epidemiological study is needed to identify the trends of gabapentin and pregabalin prescribing in a general population.
(Part 2) The overall trends were for gabapentin and pregabalin prescribing rates to rise in Tayside and Scotland from 2006 to 2016 and in Fife from 2010 to 2016. Age, SIMD, health board and some levels of rurality were associated with gabapentin and pregabalin prescribing rates. Associated mortality was higher than that in the Scottish general population which implied an association between gabapentinoids use and death rate. Further research to investigate the reasons for these findings is needed.

Keywords: **gabapentin; pregabalin; trends; rates; prescription**

1. Thesis objectives

This study aims to investigate the extent of gabapentin and pregabalin prescribing, and their associations with socio-demographic factors and subsequent health outcomes. To achieve these objectives, this study consists of two projects that are related to each other. The first stage is to conduct a systematic review to identify published evidence of gabapentinoids prescribing rates and trends, which we hope will help to quantify the scale of the issue. The second stage is to undertake data-linkage from data prepared by the Health Informatics Centre (HIC) at the University of Dundee and analyse this dataset to summarise the prescribing patterns of gabapentinoids in Tayside over 11 years (2006 to 2016) and Fife for 7 years (2010 to 2016). The association with socio-demographic factors and use of related health services will also be examined, covering two years only, using routinely available linked data from 2015 and 2016.

2. Systematic review: the prescribing rates and trends of gabapentin and pregabalin in the general population

2.1. Introduction

Gabapentinoids is a class of drug, which includes pregabalin and gabapentin (1). Gabapentin was first approved to treat epilepsy by The Food and Drug Administration (FDA) in the USA in 1993, and marketed in 1994 with the trade name Neurontin (2). Pregabalin was approved in Europe in 2004 with the trade name Lyrica (2,3). Gabapentinoids were initially introduced as a treatment for epilepsy, and now are more widely used in neurology, psychiatry and primary healthcare (4–6). Gabapentinoids are approved as the treatment for postherpetic neuralgia, neuropathic pain associated with diabetic neuropathy, fibromyalgia, and restless legs syndrome by the Food and Drug Administration (FDA) (4,7). However, in Europe, pregabalin is approved as a treatment for neuropathic pain, and as an adjunctive therapy for treatment of resistant partial epilepsy and generalized anxiety disorder, but it is not approved to treat fibromyalgia (8). In Canada, pregabalin was introduced in the early 2000s and was an antiepileptic drug (AED) with a Health Canada-approved indication for a condition other than epilepsy together with carbamazepine, valproic and topiramate, while gabapentin was only approved as a treatment for epilepsy (9). Recently, the off-label use of gabapentinoids has increased, including treatment for panic disorder, migraine prophylaxis, social phobia, mania, bipolar disorder, and alcohol withdrawal (10).

Gabapentinoids are used primarily in the treatment of chronic neuropathic pain. In Scotland, gabapentin is one of the first-line recommendations for neuropathic pain and pregabalin is in the second-line recommendations (11). Chronic pain is defined by The International Association for the Study of Pain (IASP) as, “pain without apparent biological value that has persisted beyond the normal tissue healing time (usually taken to be 3 months)” (12). The IASP defines neuropathic pain as “pain caused by a lesion or disease affecting the somatosensory system” (13). It may be caused by nerve damage (for example at surgery) or disease (for example after herpes zoster or in diabetes). A systematic review found estimated prevalence of neuropathic pain in the general population to be between 8% and 10% (14).

Gabapentinoids cross the blood–brain barrier and enter the central nervous system, binding the auxiliary α2δ subunit site of certain voltage-dependent calcium channels

(VDCCs) of neurons as inhibitors (9). This modifies the release of nerotransmitters release and decreases the excitability of nerve cells, resulting in analgesic effects in neuropathic pain (16). Generally, the recommended daily dosing of gabapentin and pregabalin for a typical adult are 1200mg-3600mg with three divided doses and 300mg-600mg with two divided doses respectively (17).

However, some problems with the use of gabapentinoids also appear. Firstly, gabapentinoids have some common side effects, such as dizziness, sedation, viral infection, visual disturbance, nystagmus, fever, drowsiness and fatigue (11,12). Secondly, the rising trend of misuse of gabapentinoids has become a concern in public health (20,21). Within Tayside Health Board, Scotland, the number of patients prescribed gabapentin and the number of prescriptions dispensed increased from 1993 to 2011, especially after gabapentin was approved for postherpetic neuralgia in 2002 (22). Thirdly, gabapentin and pregabalin can interact with some other substances, such as magnesium oxide, phenytoin, morphine, mefloquine, losartan, ethacrynic acid and caffeine, which probably cause a higher risk of side effects for patients or may reduce the therapeutic effect of each other (22,23). These concerns may result in a recommendation that the prescribing of gabapentinoids should be subject to greater control (24,25).

A study with prescribing data from Tayside, Scotland presented a significantly increasing trend of gabapentin prescribing from 2002 (22), but this study did not report the prescribing trend of pregabalin. A report from Public Health England, using the primary care prescribing medicine e-dataset, showed that the number of prescriptions for gabapentin and pregabalin were 4.9 million and 3.3 million in 2013, which means a 46% increase in the number of gabapentin prescriptions and a 53% increase for pregabalin respectively compared with 2011 (2.8 million for gabapentin prescriptions and 2.16 million for pregabalin), with the statistics of gabapentinoids prescribing varying across NHS England regions (Appendix 1) (25). The average annual increase in the number of prescriptions of gabapentinoids was approximately 24%, from around 1 million in 2004 to 10.5 million in 2015 in England and Wales (26). According to the NHS England annual prescribing cost analysis report, the number of gabapentin prescription items increased from 1,260,800 in 2006 to 6,466,482 in 2016 and the number of pregabalin prescription items increased by 11.6 times from 476,100 in 2006 to 5,547,560 in 2016 (27,28).

In the United States, the number of gabapentin prescriptions rose from 39 million in 2012 to 64 million in 2016 when gabapentin was ranked the 10th most commonly prescribed medicine (20). One study, reporting antiepileptic use for epilepsy and nonepilepsy disorders from 1998 to 2013 by using administrative health databases in Manitoba, Canada, found that gabapentin use increased 55-fold among nonepilepsy users from 0.2 per 1000 in the first quarter of 1998/1999 to 11.1 per 1000 in the last quarter of 2012/2013 (9).

An increasing gabapentinoids prescribing trend implicates a rise in the associated prescribing costs. In Scotland, the cost of pregabalin increased from £30.41 million in 2015 to £35.35 million in 2016, while the cost of gabapentin decreased from £6.92 million in 2015 to £5.58 million in 2016 (29). The investigation found that the most common reason for gabapentin and pregabalin prescribing was for epilepsy in Scotland (29). In England, the costs of gabapentin decreased from 38.1 million in 2011 to 26.7 million in 2013, while the costs of pregabalin increased from £150.7 million in 2011 to £211.2 million in 2013 (25). In the United States, pregabalin became the 8th drug listed in invoice drug spending in 2016, with costs of $4.4 billion which was almost twice the pregabalin cost in 2012 (20).

However, the gabapentinoids prescribing trends in the UK or United States cannot be mirrored in all other countries; as detailed and published evidence on the prescribing rates and trends of gabapentin and pregabalin in other countries is quite limited, the worldwide prescribing trend or rate of gabapentinoids prescribing in recent years remains unknown. Thus, with the consideration of patient safety, there is a need to summarise the gabapentin and pregabalin prescribing rates and trends in the general population, thereby resulting in a more comprehensive and stronger evidence base which will inform local and national strategies to rationalize the prescribing and safety of gabapentin and pregabalin in Scotland. Thus, this systematic review aims to summarise current published papers in relation to the prescribing rates and trends of gabapentin and pregabalin for the general population.

2.2. Methods

2.2.1. Search strategy

2.2.1.1. Pre-search

Prior to the formal search strategy being conducted, the database of Cochrane

Collaboration (CDSR) which contains systematic reviews produced by Cochrane Collaboration and PubMed was searched to gauge the existing evidence of gabapentinoids prescribing rates and trends.

After the pre-search, a structured search strategy was developed to find published and peer-reviewed articles reporting prescribing rates and trends of gabapentinoids.

2.2.1.2. Literature search

Considering the characteristics and accessibility of databases, the key electronic databases searched were MEDLINE Ovid, Embase Ovid, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, CDRS, and the Centre of Reviews and Dissemination (CDR). The CDR database contains meta-analysis and systematic reviews in medicine, including the National Health Service Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) and the Database of Abstracts of Reviews of Effects (DARE).

The search commenced December 2017 and alerts of my search for each database were set and checked for newly published results periodically until the end of 2018. Any new information of the updated results would be listed in the article if the newly published articles met the inclusion criteria of this review.

With study terms to include drug names, prescription trends and statistics decided, the systematic review team were Yiling Zhou (YZ), Jennifer Watson (JW) and Blair Smith (BS). The drug names; gabapentin and pregabalin, their most commonly known trade names (Neurontin and Lyrica, respectively), and their classification (gabapentinoids) were used in the search. For prescription, I searched using keywords, script or scripts, drug utili?ation, drug use, drug consumption and prescri*, along with their Medical Subject Headings (MeSH terms). MeSH terms included: gabapentin; pregabalin; prescription; prevalence; incidence; drug utilisation. To specify statistics, I used the following search terms; trend, rate, pattern, prevalence, incidence, number, quantity, amount, count and sum. According to the inclusion and exclusion criteria set, the year of publication was limited to 1993-current (as gabapentin was introduced in 1993); English or Chinese language were searched, and any paper that mentioned adults was included. The search strategy was concordant in each database with only tiny adjustments due to the unique feature of each database.

Our research question was specified and created by the inclusion and exclusion criteria

which were based on the Population, Intervention, Comparators, Outcomes and Study designs (PICOS) principle. However, in this study, comparator which is more appropriate in the selection criteria for clinical trial studies, was not used because this study aimed to investigate the prevalence and focused on observational studies.

2.2.1.3. Research question: *What are the trends of gabapentinoids prescribing rates in the general adult population?*

2.2.1.4. Inclusion criteria

Population

- The general population, including all people with free age range.

Intervention

- gabapentinoids
- gabapentin
- pregabalin

Outcome

- The prescribing rate (per specified time period)
- The prescribing trend (over several time periods)

Study design

- Observational study with large dataset: survey, cohort study, cross-sectional study, case control study
- Systematic review
- Meta-analysis
- Review

Language

- English and Chinese

Time period

- 1993 to current

Article type

- Peer-reviewed

2.2.1.5. Exclusion criteria

Population

- Only including children (under 18)
- Animal
- Prison population
- Post-mortem study

Outcome

- Articles only showing the misuse rate of gabapentinoids

Study design

- Case studies

Language

- Others except for English and Chinese

Time period

- Before 1993
- Articles unobtainable after review period

Article design

- Grey literature
- Non-peer reviewed

The general population data were of interest, so animal studies and papers using only populations aged under 18 were excluded. Papers focusing on prison populations and post-mortem would be excluded, because they are too specific to be representative of the general population; for example, a prison population is more likely to have substance abuse and gabapentinoids prescribing (30). However, the study population with specific age group but not only children, specific disease or exposure to specific medicine would be acceptable if they report the trends of gabapentinoids, because they are quite relevant to this systematic review except for the study population and they can provide the trends of gabapentinoids among different age groups or disease. All observational studies would be accepted except case studies, because case studies may only include several cases, from which we cannot generate a prescribing rate or reflect the prescribing pattern of the general population. Due to our resource limitation, we read English and Chinese languages, thus, papers published in other languages were excluded. The papers published in or after 1993 would be accepted, because

gabapentin was introduced in 1993. As depicted in the inclusion criteria, only peer-reviewed papers were included.

2.2.2. Paper selection

After searching each database separately, I combined all the results and imported them into Mendeley, a references-managing software. The duplications were firstly excluded by Mendeley automatically, and then were checked manually. YZ, JW and BS made up the review team. After pre-selection of a few papers following the literature searching, we discussed how to apply the inclusion and exclusion criteria to the papers. Firstly, JW and I scanned the titles independently. The citation would be excluded only when excluded by both reviewers; the remainder of citations would go to the next screening step, abstract screening. YZ and JW scanned the abstracts independently. The citation would be excluded if it was excluded by both reviewers. Editorials without new data only commenting on other studies were excluded. Following the abstract screening, the full text of the included papers was checked by the two reviewers (YZ, JW,) independently. The reference lists of included papers were checked to ensure any related papers had not been missed. During the selection process steps, if the two reviewers could not reach an agreement, a final decision on inclusion/exclusion was reached in discussion with the third reviewer, BS. The selection process steps which were followed are detailed on a flow chart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Appendix 2).

2.2.3. Data abstraction

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (Appendix 3) is a structured, standardized checklist, commonly used to assess the quality of observational studies and gives the guidelines for what should be included in an observational study. The data abstraction form in this study was designed based on the STROBE checklist, as most of the included studies are observational studies. The data abstraction form did not include all things presented by the STROBE checklist. The data abstraction form (Appendix 4) included title, abstract, introduction, methods (including study design, setting location, study period, data source, study population, which kind of gabapentinoids), results (sample size, age range, definition of outcome,

prescribing rate, prescribing trend), main findings, limitations related to prescribing trend or rate of gabapentinoids.

2.2.4. Quality assessment

Quality assessment tools are used to ensure the results of the systematic review capture and summarise the quality of evidence. All included papers were observational studies, and the quality assessment tool in this systematic review was designed based on two existing quality assessment tools: the National Heart, Lung and Blood Institute (NHLBI) (Appendix 5) which is a quality assessment tool widely used for Cohort and Cross-sectional studies; and the quality criteria for critical appraisal of observational studies which was adapted from the CRD handbook (Appendix 6).

2.2.5. Data summary

The final selected papers were summarised in tables according to the study type. The tables were designed based on the characteristics of the study design type: cross-sectional studies, cross-sectional time series studies and cohort studies. Due to there being too much information from cross-sectional study to summarise, two kinds of tables were designed to summarise the information: one was to summarise the demographic information, and the other was to summarise the definition of interest outcome, prevalence and main findings. For cohort studies and cross-sectional time series studies, one table was designed for each type of study, including demographic information, definition of interest outcome, prevalence and main findings. The demographic information contained the basic information about the study (author, country, published year, study period), study population (size, clinical status, age, exposure, cohorts), data source and exposure (gabapentin, pregabalin or both). Main findings mainly included the prescribing trends and associated demographic factors. Limitations were also summarised for each study, but they would be discussed in the Discussion section, not listed in the summary table.

2.3. Results

2.3.1. Characteristics of studies

We identified 529 articles from the key medical databases after excluding duplication (Figure 1). These articles were then either included or excluded after being reviewed by title, abstract and full text according to the selection criteria.

After reviewing the abstracts, there were 71 papers identified for full text review. Of these 12 papers proved to be conference abstracts and were thus excluded, according to the review protocol. Therefore, we had 59 papers with full text for review. Six articles were selected for full text review from manually checking the reference lists of the 59 papers for full text review. Any papers which only reported on a study population aged under 18, only focusing on a specific population, such as patients during status epilepticus period, failure to mention gabapentinoids prescribing, or focusing on the treatment and lacking comparable trends in different periods were excluded at the step of full text screening (Figure 1).

The manual reference checking step found three potential papers (from the six papers included in the first reference checking). However, two papers only studied the population aged under 18, and one paper only investigated the gabapentin prescribing proportion, lacking the prescribing trend. Thus, these three papers were excluded.

Finally, 17 papers were selected for data abstraction and quality assessment. Among the 17 papers, there were 13 cross-sectional studies (8,31,40–42,32–39), two cross-sectional time series studies (43,44), and two cohort studies (45,46). Among these 17 papers, ten papers were published after 2013 and the earliest one was published in 2007. All 17 papers were written in English and we did not find any Chinese articles when we searched the selected databases using the search strategy.

The size of study population among the 17 papers varied from 2,163 (42) to 4,985,870 (38). The age ranges of study populations were also different; such as all age range, aged 15 or over, all adults, aged 20 or over, aged 60 or over and aged 65 or over. For the country setting, both of the cross-sectional time series studies were from Canada (43,44); and the two cohort studies, were from USA (45) and the UK (46). Among the cross-sectional studies, there were five papers from Italy (31,32,34,36,42), three papers from Norway (35,38,41), and one paper each from Scotland (33), Sweden (8), Taiwan (China) (39), Australia (37) and New Zealand (40). The study period of the 17 papers varied from 2 years (33) to 15 years (47). (Tables 1 –3).

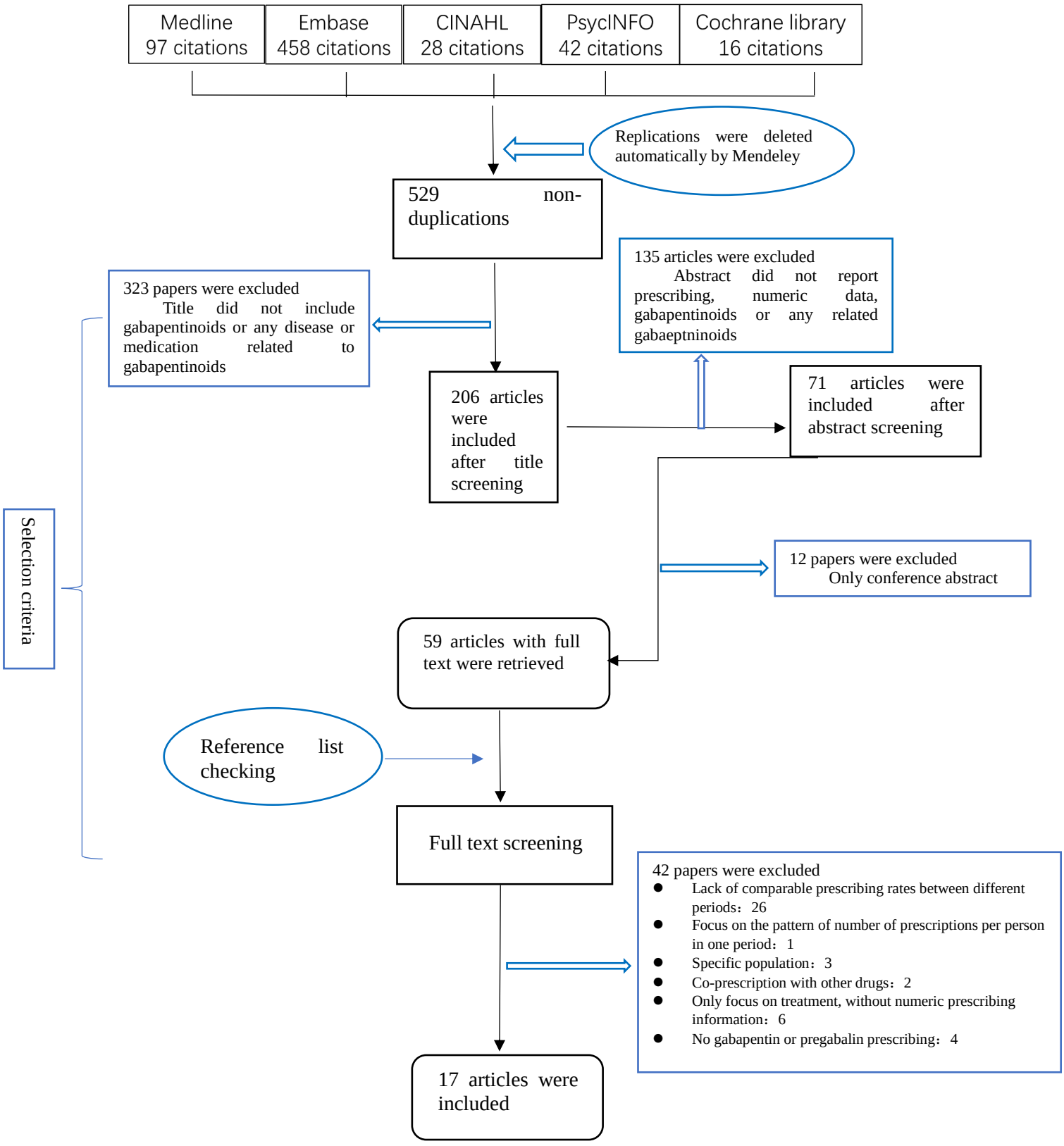

Figure 1. Flow chart of study selection

2.3.2. Cross-sectional studies

Table 1-a summarises the demographic information and Table 1-b summarises the definition, prevalence and main findings from the 13 cross-sectional papers. Among the 13 papers, there were nine papers studying both pregabalin and gabapentin (31–38,42), three papers only mentioning gabapentin (39–41) and one paper focusing on pregabalin (8). The majority of the 13 papers used the general population with different age ranges, while the paper written by Alessandro et al (34) studied patients prescribed at least one AED and who were aged 65 or over. The paper written by Prasad et al (40) studied patients who were aged 65 or over whereas for the paper written by Galimberti et al (42), the study population were the residents in 21 nursing homes. Additionally, the definition of exposures used by these papers was different. For example, some papers used the exposure, commencing gabapentin or pregabalin prescription during the study period (31–33,45,46), while others used exposure as prescribed at least one gabapentin or pregabalin during the study period. The differences of the study population and exposure choice make the results difficult to synthesize.

The definitions of the outcome of interest were dissimilar, mainly dependent on how the data were collected. To quantify the gabapentin or pregabalin prescribing, there were seven papers using the WHO defined daily dose (DDD) (31,34,35,37,38,40,41). (The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults). Two papers used the proportion of number of patients who were prescribed gabapentin or pregabalin (8,33), two papers used the number of patients prescribed gabapentin or pregabalin (39,42), three papers used prescribing incidence (31,32,34) and two papers used prevalence rates (34,36,39). Some papers reported more than one outcome to quantify the gabapentin or pregabalin prescribing (31,34,39).

One paper from Taiwan, China (39) aimed to evaluate the prevalence of prescription and use of antiepileptic drugs (AEDs) for the treatment of epilepsy in a nationwide population, which included gabapentin and pregabalin. Thus, in this study, it included the prevalence of gabapentin prescription in a nationwide population in Taiwan from 2003 to 2007 and it also compared the prevalence among patients with epilepsy, pain disorder and psychiatry. It was found that the total number of gabapentin users each

year increased from 2003 (256) to 2007 (820). This study also found that the proportion of gabapentin prescriptions increased slightly from 2003 to 2006 and then decreased slightly in 2007 among patients with epilepsy (2.5% - 3%) and psychiatry (2% - 4%), while the proportion among patients with pain disorder increased significantly from 8% (2003) to 28% (2007). Another finding was that older patients aged 55 and over were the age group that was prescribed gabapentin most often (around 47.7% to 68.6 %) amongst patients receiving gabapentin each year.

One study from Norway conducted by Landmark et al (41) aimed to investigate how AEDs were used at the National Centre for Epilepsy in Norway, providing a graphical presentation about the trends of gabapentin use in Norway from 1996 to 2005. The number of DDDs of gabapentin in Norway increased gradually from <0.1 per 1,000 persons per day in 1996 to around 1.2 in 2004 and then slightly decreased to 1.1 in 2005. Another study conducted in Norway (38) found the number of DDDs per 1,000 persons per day of pregabalin increased slightly from 2008 (2.07) to 2012 (2.23), and the number of DDDs of gabapentin increased from 0.75 in 2008 to 1.9 in 2012. Another study undertaken in Norway (35) calculated the number of DDDs per 1,000 persons per day of gabapentin and pregabalin among patients with neuropathic pain, epilepsy and psychiatric illness respectively using the data from the Norwegian prescription database and statistics Norway during 2004 to 2015. It was found that, amongst patients with psychiatric illness, the number of DDDs of pregabalin increased from less than 0.01 in 2008 to 0.18 in 2015 per 1,000 persons per day and for patients with epilepsy, the number of DDDs of pregabalin increased from 0.01 per 1,000 persons per day in 2005 to 0.5 in 2012. Among patients with neuropathic pain, the number of DDDs per 1,000 patients per day of gabapentin in 2015 (4.8) was over 11 times that in 2004 (0.35). However, this study only studied patients who were aged 60 or over.

One study from Sweden (8) aimed to assess prescribing patterns, sociodemographic characteristics and previous disease history in patients receiving pregabalin. The study used the proportion of patients who were prescribed pregabalin at least once to present the pregabalin prescribing rate. It was found that the prescribing rate increased for both women and men, and that the increase for women (2.2% in 2006 to 7% in 2009) was greater than that for men (1.5% in 2006 to 4.2% in 2009). This study also reported that women were prescribed pregabalin more frequently than men.

One paper from Italy (32) aimed to analyse the prescribing patterns of both newer and older AEDs. This study selected all people aged over 15 in Caserta and used yearly incidence figures to describe the gabapentin or pregabalin prescribing rate each year. This study found that, compared with the incidences in 2005 (50.7 per 1,000 persons for gabapentin and 29.2 per 1,000 persons for pregabalin), the incidence of gabapentin decreased dramatically in 2011 (9.3 per 1,000 persons), while the incidence of pregabalin increased significantly in 2011 (42.2 per 1,000 persons). Another study from Italy (36) aimed to evaluate the prevalence of prescribing patterns of AEDs in Italian general practice. A one-year prevalence rate was used to describe gabapentin and pregabalin prescribing. It was found that the prevalence of gabapentin use increased gradually from 0.4 per 1,000 persons in 2000 to 8 per 1,000 persons in 2004 and then slightly decreased to 7.5 per 1,000 persons in 2005. The same study found the prevalence of pregabalin prescribing in 2005 was 2.5 per 1,000 persons, as pregabalin was only generally marketed from 2004 in Italy. Another paper in Italy (34) found the incidence of gabapentin decreased from 12.5% in 2004 to 2.6% in 2007, while the incidence of pregabalin increased from 5.5% in 2005 to 6.7% in 2007. The prevalence of pregabalin prescribing fluctuated from 2005 to 2007 (7.3% in 2005, 25.2% in 2006, 13.1% in 2007). The number of DDDs of gabapentin prescribed per 1,000 persons decreased from 1.66 in 2005 to 0.94 in 2007, while for pregabalin, it fluctuated during 2005 to 2007, 0.25 in 2005, 1.51 in 2006 and 1.03 in 2007. However, this study only included patients who received at least one AED and were aged 65 or over. Another Italian study (31) found the incidence of gabapentin prescribing decreased from 5.53% in 2004 to 4.73% in 2005, and the number DDDs of gabapentin prescribed per 1,000 persons per day fluctuated: 0.6 in 2003, 0.55 in 2004 and 0.59 in 2005. The final study in Italy (42) found 68 patients were prescribed gabapentin and 19 patients were prescribed pregabalin in 2012 compared with no patients being prescribed gabapentin or pregabalin in 2000, but this study only included 2,163 patients resident in a nursing home.

The paper from Australia (37) studied all patients entered in the Medicare Australia and Drug Utilisation Sub-Committee database and found the number of prescribed DDDs of gabapentin increased slightly from 2003 to 2007 (0.43 to 0.49 per 1,000 persons per day). The trend with pregabalin also increased from 2005 to 2007 (0.03 to 0.18 per 1,000 persons per day). The paper from New Zealand (40) found the number of

prescribed DDDs of gabapentin increased dramatically from 0.35 in 2005 to 1.37 in 2006 and rose steadily to 1.58 in 2008 and then decreased gradually to 0.05 in 2010, then declined slightly to 0.04 in 2013 (per 1,000 persons per day) among all people aged over 65. The paper from Scotland found the proportion of patients who were prescribed gabapentin and pregabalin was much greater in 2010 (1.2 % for gabapentin and 0.26% for pregabalin) than that in 1995 (0.02 % for gabapentin and less than 0.1% for pregabalin) among patients aged 20 or over (33).

Table 1-a. Summary of gabapentinoid prescribing trends or rates in cross-sectional studies-demographic information

Study	Study population	Exposure	Data source
Baftiu et al (35) 2017 Norway 2004-2015	883,323 in 2004, 1,013,855 in 2010, 1,121,796 in 2015. All people >=60 years old	Gabapentin and pregabalin	Norwegian prescription database and statistics Norway
Nishtala et al (40) 2016 New Zealand 2005-2013	20,370 in 2005, 25,932 in 2013. All people aged 65 and over.	Gabapentin	New Zealand Ministry of Health
Baftiu et al (38) 2016 Norway 2008-2012	4,737,200 in 2008, 4,799,252 in 2009, 4,858,199 in 2010, 4,920,305 in 2011, 4,985,870 in 2012 All people aged from 0 to 103	Gabapentin and pregabalin	Norwegian prescription database
Italiano et al (32) 2015 Italy 2005-2011	168,397 inhabitants aged >=15 years old and registered in 123 GPs	Gabapentin and pregabalin	Arianna database
Wettermark et al (8) 2014 Sweden 2005-2009	Around 2 million inhabitants in Stockholm	Pregabalin	Swedish prescribed drug register, National patient register, the cause of death register, the regional primary care database of Stockholm County Council, Statistics Sweden
Ruscitto et al (33) 2014 Scotland 1995 and 2010, two years	301,020 in 1995 311,881 in 2010 All people >=20 registered in GP in Tayside	Gabapentin and pregabalin	Health informatics centre database
Hsieh et al (39) 2011 Taiwan (China) 2003-2007	About 600,000 in the random sample of NHIRD cohort. All people, and people aged 18 or over were also selected out.	Gabapentin	The national health insurance research database
Hollingworth et al (37) 2009 Australia 2002-2007	All people obtained in the database	Gabapentin and pregabalin	Medicare Australia and Drug Utilisation Sub-Committee database
Alacqua et al (31) 2009 Italy 2003-2005	127,389 patients registered in 93 GPs in the Arianna database during 2003-2005 All people aged >=15	Gabapentin and pregabalin	Arianna database
Oteri et al (34) 2009 Italy 2004-2007	17,071 elder people, 1,609 received at least one AED. People over 65, receiving at least 1 AEDs.	Gabapentin and pregabalin	The Caserta-1 local-health-unit Arianna databases
Savica et al (36) 2007 Italy 2000-2005	465,061 people All individuals registered in the 320 GPs` lists. All people aged 15 and over	Gabapentin and pregabalin	Health search database
Landmark et al (41) 2007 Norway 1993-2004	The whole population in Norway	Gabapentin	N/A
Galimberti et al (42) 2015 Italy 2000 and 2012, two years	2,163 residents in 21 nursing home Aged 60 or over	Gabapentin and pregabalin	Collected by the study group, local physicians and health managers

Table 1-b. Summary of gabapentinoid prescribing trends or rates in cross-sectional studies-main findings

Study	Definition	Prevalence	Main findings
Baftiu et al (35) 2017 Norway 2004-2015	DDDs= sum of DDDs subgroup (epilepsy, neuropathic pain or psychiatry disorder) *1000/365*number of inhabitants aged 60 or over in Norway (per 1000 persons per day)	Epilepsy: Pregabalin: 0.01 in 2005, over 0.5 in 2012, below 0.5 in 2013, slightly above 0.5 in 2015 Gabapentin: 1.3 in 2004, 0.15 in 2012, 0.25 in 2013, 0.21 in 2015. Neuropathic pain: Pregabalin: (0.01) 2004, 2009 (3.1), 2010 (2.8), 2015 (4.3). Gabapentin: (0.35)2004, 2015 (4.8). Psychiatry: Pregabalin: over 0 in 2008, 2012 (0.18), 2015 (about 0.18).	Epilepsy: Pregabalin: increase from 2005 to 2012, and decrease from 2012 to 2013, then increase from 2013 to 2015. Gabapentin: decrease from 2004 to 2012, and increase in 2013, then decrease from 2013 to 2015. Neuropathic pain: Pregabalin: increase from 2004 to 2009, decrease in 2010, then increase from 2010 to 2015. Gabapentin: increase from 2004 to 2015. Psychiatry: Pregabalin: increase from 2008 to 2012, and decrease in 2013, then increase from 2013 to 2015.
Nishtala et al (40) 2016 New Zealand 2005-2013	The WHO defined daily dose (DDD) method was used to describe the number of older people on a defined standard daily dose per thousand older people (>=65 years) per day (TOPD) (per 1000 persons per day)	0.35 in 2005, 1.37 in 2006, 1.52 in 2007, 1.58 in 2008, 1.00 in 2009, 0.05 in 2010, 0.05 in 2011, 0.04 in 2012, 0.04 in 2013.	2005 to 2008 increase, 2008 to 2013 decrease
Baftiu et al (38) 2016 Norway 2008-2012	The utilisation of AEDs is presented as DDDs/1000 inhabitants/day	Pregabalin: 2.07 in 2008, 2.1 in 2009, 2.11 in 2010, 2.21 in 2011, 2.23 in 2012 Gabapentin: 0.75 in 2008, 1.25 in 2009, 1.65 in 2010, 1.8 in 2011, 1.9 in 2012.	The DDDs of pregabalin increased from 2008 to 2012. The DDDs of gabapentin increased from 2008 to 2012.
Italiano et al (32) 2015 Italy 2005-2011	Yearly incidence = the number of new users /the number of inhabitants alive and registered in the GPs` lists and who were free from any AED prescription in the previous year. New user was defined as a patient receiving a first AED during the observation period, without any recorded AED prescription in the previous 365 days. (per 1000 inhabitants)	Gabapentin: 50.7 in 2005, 9.3 in 2011. Pregabalin: 29.2 in 2005, 42.2 in 2011.	Incidence of gabapentin decreased dramatically in 2011 compared with 2005 Incidence of pregabalin increased significantly in 2011 compared with 2005
Wettermark et al (8) 2014 Sweden 2005-2009	The proportion = number of patients in the region dispensed at least one prescription of pregabalin each year per 1000 inhabitants between 6/2005 to 12/2009. (%)	Women around 2.2, men 1.5(2006) Women around 4.5, men 2.8(2007) Women around 6.1, men 3.7(2008) Women around 7, men 4.2 (2009)	From 2006 to 2009, the prescribing rate for both women and men increased

* DDDs= sum of DDDs *1000/365, per 1000 persons per day, means the daily defined dose.

Table 1-b cont`d. Summary of gabapentinoid prescribing trends or rates in cross-sectional studies-main findings

Study	Definition	Prevalence	Main findings
Ruscitto et al (33) 2014 Scotland 1995 and 2010 two years	The portion of patients who currently prescribed gabapentin or pregabalin. Current prescribing defined as receiving a dispensed medication in the 84 preceding (and including) 31 March 1995 and 31 March 2010.	Gabapentin: 54 patients (0.02%) in 1995, 3,682 patients (1.2%) in 2010 Pregabalin: 0 in 1995, 800 patients (0.26%) in 2010	Gabapentin increase in 2010 compared with 1995 Pregabalin increase in 2010 compared with 1995
Hsieh et al (39) 2011 Taiwan (China) 2003-2007	Number of patients who prescribed gabapentin.	Number of patients: 256 in 2003, 416 in 2004, 538 in 2005, 674 in 2006, 820 in 2007	The total number of gabapentin users increase from 2003 to 2007. Older people are more likely to prescribe gabapentin (>=55). Male people are more likely to prescribe gabapentin than female.
Hollingworth et al (37) 2009 Australia 2002-2007	DDD per 1000 population per day. (1000 inhabitants per day)	Gabapentin: 0.43 in 2003, 0.48 in 2005, 0.49 in 2007. Pregabalin: 0.03 in 2005, 0.18 in 2007.	The amount of gabapentin used increased from 2003, 2005 to 2007, and the amount of pregabalin used increased between 2005 and 2007
Alacqua et al (31) 2009 Italy 2003-2005	1. incidence = the number of new users/ the number of subjects alive and registered in the GPs` lists. (per 1000 persons) New users are defined as patients receiving at least one AED prescription in the observation year, without any recorded AED prescription in the previous one. 2. DDD per 1000inhabitants/day.	Incidence: Pregabalin, 2.18 in 2005 Gabapentin, 5.53 in 2004, 4.73 in 2005. DDD Gabapentin: 0.6(2003), 0.55(2004), 0.59(2005). Pregabalin:0.07 (2005) (per 1000 persons per day)	The incidence of gabapentin decreases from 2004 to 2005. The volume of gabapentin decreases from 2003 to 2004 and then increases from 2004 to 2005.
Oteri et al (34) 2009 Italy 2004-2007	1. One-year prevalence of gabapentin (pregabalin) = the ratio between the number of patients who received >=1 gabapentin (pregabalin) and the number of subjects alive and registered in the GP`s lists, for each year. (per 1000inhabitants) 2. Incidence of gabapentin (pregabalin) = the number of new user / the number of subjects free from AED prescription in the previous year. New user= a patient receiving at least one gabapentin (pregabalin) during the observational year, without any record gabapentin(pregabalin) prescribed in the previous one. (Rates per 1000inhabitants) 3. DDD per 1000 inhabitants per day.	1. Prevalence: pregabalin 7.3 (6-8.6) in 2005, 25.2(22.8-27.5) in 2006, 13.1 (11.4-14.8) in 2007. 2. Incidence: Gabapentin, 12.5 in 2004 (10.8-14.2), 9.7 in 2005, 7.6 in 2006, 2.6 (1.8-3.4) in 2007 Pregabalin, 5.5 (4.4-6.6) in 2005, 18.1 (16.1-20.2) in 2006, 6.7(5.5-8.0) in 2007 3. DDD: Gabapentin, 1.58 in 2004, 1.66 in 2005, 1.35 in 2006, 0.94 in 2007. Pregabalin, 0.25 in 2005, 1.51 in 2006, 1.03 in 2007.	1. Among newer AED, gabapentin was the most prescribed drug until 2005. Pregabalin, marketed in Italy in 2004, overcame gabapentin use during 2006 and 2007. Pregabalin prescribing increase from 2005 to 2006, followed a reduction in 2007. 2. Incidence Gabapentin, decrease from 2004 to 2007 Pregabalin, increase from 2005 to 2006 and decrease from 2006 to 2007 3. DDD Gabapentin, increase from 2004 to 2005, decrease from 2005 to 2007 Pregabalin, increase from 2005 to 2006 significantly, decrease from 2006 to 2007.

* DDDs= sum of DDDs *1000/365, per 1000 persons per day, means the daily defined dose.

Table 1-b cont`d. Summary of gabapentinoid prescribing trends or rates in cross-sectional studies-main findings

Study	Definition	Prevalence		Main findings
R.Savica et al (36) 2007 Italy 2000-2005	1-year prevalence = the number of gabapentin or pregabalin users/ the number of subjects alive and registered in the GP lists per year (per 1000 inhabitants)	Gabapentin: Pregabalin:	0.4 in 2000, 1.8 in 2001, 5.1 in 2002, 7.6 in 2003, 8.0 in 2004, 7.5 in 2005. 2.5 in 2005.	The prevalence of gabapentin using increased from 2000 to 2004 and then slightly decreased.
Landmark et al (41) 2007 Norway 1993-2004	DDD (per 1000 inhabitants)		N/A	The DDD of Gabapentin increased from 1993 to 2003, and then decreased from 2003 to 2004.
Galimberti et al (42) 2015 Italy 2000and 2012 two years	the number of patients who prescribed at least one gabapentin (pregabalin)	Gabapentin: Pregabalin:	<0.001 in 2000, 67.8 in 2012. <0.01 in 2000, 18.9 in 2012.	The number of patients in this study population increased in 2012 compared with that in 2000

* DDDs= sum of DDDs *1000/365, per 1000 persons per day, means the daily defined dose.

2.3.3. Cross-sectional time series studies

The two cross-sectional time series studies were summarised in Table 2. Kwok et al (44) studied pregabalin but not gabapentin. The study aimed to identify the effect of change of medicine policy on pregabalin use and the characteristics of new patients commencing pregabalin under the expanded access. The study population was all Ontario Drug Benefit (ODB)-eligible individuals. This study used the proportion of patients who were prescribed pregabalin to quantify the rate of pregabalin prescribing and compare the trends of pregabalin prescribing between ODB-eligible patients aged under 65 and ODB-eligible patients 65 and older. It was found that the rate of pregabalin prescribing in 2014 (19.7) was 22-fold times more than that in 2006 (0.89) (per 1,000 ODB-eligible patients), and nearly 30 times more than that in 2013 (0.7) among ODB-eligible patients 65 and older. Among the ODB-eligible patients under 65, the rate of pregabalin increased gradually from 0.1in 2006 to 1.8 in 2013 and soared to 28.6 in 2014 (per 1,000 ODB-eligible patients). It also found that the rate of pregabalin in the younger age group was consistently greater than in the older age group.

Leong et al (43) studied gabapentin prescribing in Manitoba, Canada and the study period was over 15 years (1998-2013). The objective of this study was to identify the trends in AED use in Manitoba. As gabapentin was also used to treat epilepsy, it was included as an AED in this study. This study compared the prevalence of gabapentin prescribing between epileptic patients and non-epileptic patients. It was found the prevalence of gabapentin had a 55-fold increase from 0.2 in the first quarter of 1998 to 11.1 in the last quarter of 2013 among non-epileptic patients (per 1,000 persons), while it was relatively stable among epileptic patients (around 25 per 1,000 persons) and the prevalence of gabapentin prescribing among epileptic patients was consistently greater than among non-epileptic patients. The results could reflect the gabapentin use in the Manitoba general population from 1998 to 2013. However, the results were only shown graphically as line charts, so this study failed to provide the exact value for the prevalence of gabapentin use.

Table 2. Summary of gabapentinoids prescribing trends or rates in cross-sectional time series studies

Study (author, published year, country)	**study period**	**study population (study size, age, clinical status)**	**exposure**	**data source**	**Definition**	**Prevalence**	**Main findings**
Kwok et al (44) 2017 Canada	1/4/2006 to 31/12/2014	108,047 between 2006 and 2014. All ODB-eligible individuals who were dispensed a pregabalin.	Pregabalin	The Ontario Drug Benefit (ODB) database and Health Information Discharge Abstract Database	The rate of pregabalin = the number of patients who prescribed pregabalin / the total ODB eligible patients each year	0.1 in 2006, 1 in 2013, 22 in 2014. (per 1000 ODB eligible people)	Increase from 2006-2014， 22-fold increase in 2014 compared with 2013.
Leong et al (43) 2016 Canada	1998-2013	1.2 million individuals living in Manitoba	Gabapentin	Administrative health databases in Manitoba	Prevalence every 3 months in subgroup= the number of individuals filling a prescription for gabapentin or pregabalin/ the total number of individuals with (without) epilepsy and alive in Manitoba at the beginning of the given interval (per 1000 individuals)	0.2 in first quarter of 1998/1999, 11.1 in the last quarter of 2012/2013 among nonepilepsy AEDs users (per 1000 persons)	For individuals without epilepsy, the prevalence of gabapentin increased dramatically from 1998 to 2013 (55-fold increase). For individuals with epilepsy, the prevalence of gabapentin fluctuated at the level, around 25 users per 1000 inhabitants from 1998 to 2013.

2.3.4. Cohort studies

The two cohort studies are summarised in Table 3. Of the two papers, one paper (46), of which the objectives were related to our study, was to update the incidence rates and prescribing practices for neuropathic pain in a UK population, while the other paper (45) focused on examining medication adherence and healthcare costs for combination prescribing and monotherapy initiators in South Carolina, but it also reported related information about pregabalin prescribing. Marlow et al only studied pregabalin (45), while Hall et al studied both pregabalin and gabapentin (46). The study periods of the two papers were both six years, but the selection of study populations was quite different. The study by Hall et al, undertaken in the UK (46), studied the general population, while the paper written by Marlow et al in USA (45) reported a specific population with only 1,881 patients who were diagnosed with fibromyalgia and commenced at least one of the listed drugs, Duloxetine, Milnacipran, Venlafaxine and Pregabalin.

The cohort study written by Hall et al (46) used the number of patients with a first gabapentin or pregabalin prescription to quantify the gabapentinoids prescribing. It was found that the number of patients prescribed gabapentin and pregabalin both increased from 2005 to 2010 in the study population: for gabapentin (4,210 patients in 2006 to 7,207 patients in 2010); for pregabalin (2,719 patients in 2006 to 5,416 patients in 2010).

In the paper by Marlow et al (45), even though the main objective was not about pregabalin prescribing, they did report some information about pregabalin prescribing. This paper found the number of patients commenced on pregabalin fluctuated between 2006 and 2011, varying from 158 to 738.

Table 3. Summary of gabapentinoids prescribing trends or rates in cohort studies

Study (authour, published year, country)	**study period**	**study population (study size, age, clinical status)**	**Study drug of gabapentinoid**	**data source**	**Definition**	**Prevalence**	**Main findings**
Marlow et al (45) 2017 USA	2006-2011	1881 People with Fibromyalgia Syndrome (FMS), initiate 1 of 4 prescription medication therapies, duloxetine/milnacipran/venlafaxine /pregabalin	Pregabalin	Population-based administrative claims data for FMS patients in South Carolina	The number of patients who initiated pregabalin. Medication initiation was defined as no prescription coverage for medication in the prior 90 days, and the index date was defined as the medication initiation date. The year is the initiate index year.	2007 (164), 2008 (304), 2009 (209), 2010 (738), 2011 (612).	Increase from 2007 to 2008, decrease from 2008 to 2009, then increase from 2009 to 2010, and then decrease from 2010 to 2011
Hall et al (46) 2013 UK	2005-2010	All patients who were permanently registered at a GPRD practice at any time from 1/1/2005 to 31/12/2010 All age.	Gabapentin and pregabalin	General practice research database	The number of patients with first prescriptions of gabapentin or pregabalin in each year.	Gabapentin: 4,210 in 2006, 5,433 in 2007, 6,083 in 2008, 6,938 in 2009, 7,207 in 2010. Pregabalin: 2,719 in 2006, 2,979 in 2007, 3,652 in 2008, 4,333 in 2009, 5,416 in 2010.	The number of patients with first prescription of gabapentin increased from 2006 to 2010. The number of patients with first prescription of pregabalin increased from 2006 to 2010.

2.3.5. Quality assessment

There were five papers of high quality, nine papers of medium quality and three papers of low quality, summarised in Table 4. The nine papers of medium quality included obvious limitations. Among these nine papers, the study period was a limited number of years. For example, the paper written by Alacqua et al (31) only reported gabapentin prescribing rates in 2004 and 2005, and pregabalin prescribing rate in 2005, failing to provide the trends over years. The other one written by Ruscitto et al (33) only compared the number of patients who were currently prescribed gabapentin or pregabalin between two years, 1995 and 2010, so it was not able to show the annual change over the 15 year period in Tayside, Scotland. Among the three papers of low quality, Galimberti et al (42) only compared the number of patients who were prescribed gabapentin and pregabalin between two years, 2000 and 2012, but again did not present the changes during the 12 year period. The patients who were identified as being prescribed gabapentinoids in 2000 were from an earlier study conducted by the same researcher and this paper failed to report these details. Thus, the results lacked validity and it was marked low quality. Hollingworth et al (48) failed to give the sample size and details of study population and only examined two years, so again it lacked internal and external validity. The final paper by Landmark et al (41) with low quality failed to give the information about the study population and data source, so it was marked as low quality.

Table 4. Quality assessment of observational studies

Assessment questions	**Baftiu et al** (35)	**Nishtala et al** (40)	**Baftiu et al** (38)
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y
3. Were the study participants adequately described? For example, look for adequate descriptive data on age, sex, baseline health status, and other relevant variables.	N	N	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y
5. Were objective, standard criteria used for measurement of condition?	Y	Y	Y
6. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	Y	Y
7. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y
8. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y
9. Were the measures used in the study the most relevant ones for answering the research question?	Y	Y	Y
10. Was the study long enough, and large enough to allow changes in the outcome of interest to be identified?	Y	Y	Y
11. Was the outcome assessment blind to exposure status?	Y	Y	Y
Other comments	The study population only included people aged 60 or over; The results failed to give the exact value.	The study population only included patients aged 65 or over;	It failed to give the exact value, only gave the bar chart.
Overall quality rating	M	M	H

*Y yes, N no, H high quality, M mediate quality, L low quality, NA not applicable, NR not reported.

Table 4 cont`d. Quality assessment of observational studies

Assessment questions	**Italiano et al** (32)	**Wettermark et al** (8)	**Ruscitto et al** (33)
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y
3. Were the study participants adequately described? For example, look for adequate descriptive data on age, sex, baseline health status, and other relevant variables.	Y	Y	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y
5. Were objective, standard criteria used for measurement of condition?	Y	Y	Y
6. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	Y	Y
7. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y
8. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y
9. Were the measures used in the study the most relevant ones for answering the research question?	Y	Y	Y
10. Was the study long enough, and large enough to allow changes in the outcome of interest to be identified?	Y	Y	N
11. Was the outcome assessment blind to exposure status?	Y	Y	Y
Other comments			It only reported the rates of prescribing for two years
Overall quality rating	H	H	M

*Y yes, N no, H high quality, M mediate quality, L low quality, NA not applicable, NR not reported.

Table 4 cont`d. Quality assessment of observational studies

Assessment questions	**Hsieh et al** (39)	**Hollingworth et al** (37)	**Alacqua et al** (31)
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y
3. Were the study participants adequately described? For example, look for adequate descriptive data on age, sex, baseline health status, and other relevant variables.	N	N	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y
5. Were objective, standard criteria used for measurement of condition?	Y	Y	Y
6. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	Y	Y
7. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y
8. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y
9. Were the measures used in the study the most relevant ones for answering the research question?	Y	Y	Y
10. Was the study long enough, and large enough to allow changes in the outcome of interest to be identified?	Y	N	N
11. Was the outcome assessment blind to exposure status?	Y	Y	Y
Other comments	Only including the patients who prescribed gabapentin for at least two times; prevalence only showed read by bar chart, lack of exact value.	lack of sample size and age information; only studied only three or two years.	The study period only last for 3 years for gabapentin, while only one year for pregabalin
Overall quality rating	M	L	M

*Y yes, N no, H high quality, M mediate quality, L low quality, NA not applicable, NR not reported

Table 4 cont`d. Quality assessment of observational studies

Assessment questions	**Oteri et al** (34)	**Savica et al** (36)	**Landmark et al** (41)
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y
3. Were the study participants adequately described? For example, look for adequate descriptive data on age, sex, baseline health status, and other relevant variables.	N	Y	N
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y
5. Were objective, standard criteria used for measurement of condition?	Y	Y	Y
6. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	Y	Y
7. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y
8. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y
9. Were the measures used in the study the most relevant ones for answering the research question?	Y	Y	Y
10. Was the study long enough, and large enough to allow changes in the outcome of interest to be identified?	Y	Y	Y
11. Was the outcome assessment blind to exposure status?	Y	Y	Y
Other comments	The study population only included people aged over 65		There was no information about the study population and sample size; It failed to give the data source and the exact value for DDDs
Overall quality rating	M	H	L

*Y yes, N no, H high quality, M mediate quality, L low quality, NA not applicable, NR not reported.

Table 4 cont`d. Quality assessment of observational studies

Assessment questions	**Galimberti et al** (42)	**Hall et al** (46)	Marlow et al (45)
1. Was the research question or objective in this paper clearly stated?	Y	Y	Y
2. Was the study population clearly specified and defined?	Y	Y	Y
3. Were the study participants adequately described? For example, look for adequate descriptive data on age, sex, baseline health status, and other relevant variables.	N	N	N
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	Y
5. Were objective, standard criteria used for measurement of condition?	Y	Y	Y
6. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	Y	Y
7. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y
8. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y
9. Were the measures used in the study the most relevant ones for answering the research question?	Y	Y	Y
10. Was the study long enough, and large enough to allow changes in the outcome of interest to be identified?	N	Y	Y
11. Was the outcome assessment blind to exposure status?	Y	Y	Y
Other comments	It only included a two-year prescribing trend and it failed to give the details about earlier year;	The study population only included patients who commence pregabalin or gabapentin.	The study population only included patients who commence pregabalin

Overall quality rating	L	M	M

*Y yes, N no, H high quality, M mediate quality, L low quality, NA not applicable, NR not reported.

Table 4 cont`d. Quality assessment of observational studies continue

Assessment questions	**Kwok et al** (44)	**Leong et al** (43)
1. Was the research question or objective in this paper clearly stated?	Y	Y
2. Was the study population clearly specified and defined?	Y	Y
3. Were the study participants adequately described? For example, look for adequate descriptive data on age, sex, baseline health status, and other relevant variables.	Y	Y
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y
5. Were objective, standard criteria used for measurement of condition?	Y	Y
6. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	Y	Y
7. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y
8. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y
9. Were the measures used in the study the most relevant ones for answering the research question?	Y	Y
10. Was the study long enough, and large enough to allow changes in the outcome of interest to be identified?	Y	Y
11. Was the outcome assessment blind to exposure status?	Y	Y
Other comments	The generalizability for the results is restricted to the elderly with low socioeconomic status.	It failed to give the exact value for prevalence and the prevalence could only be roughly read from line chart.

Overall quality rating	M	H

*Y yes, N no, H high quality, M mediate quality, L low quality, NA not applicable, NR not reported.

2.4. Discussion

The number of gabapentinoids prescriptions increased from 1 million in 2004 to 10.5 million in 2015 in England and Wales (26). In Scotland, according to the Information Services Division (ISD) electronic data, the number of pregabalin prescription items increased significantly from 27,094 in 2006 to 435,498 in 2016, while the number of gabapentin prescription items decreased slightly from 308,313 in 2010 to 302,736 in 2011, then rose up to 694,293 in 2016. In this systematic review, it was found that the prescribing rates and trends differed in different countries (Figure 2-a and Figure 2-b).

The number of patients prescribed at least one gabapentin increased in UK (46), Taiwan (39) and Italy (42) during their study periods, while three other papers in Italy (31,32,34) found the incidence of gabapentin prescribing decreased in each of their study periods (Figure 2-a). Two papers from Norway (38,41) found the numbers of DDDs of gabapentin increased during their study periods, while another Norwegian paper (35) found this decreased dramatically from 1.1 in 2007 to 0.25 in 2009 among patients with epilepsy (per 1,000 persons per day). The study in New Zealand (40) found the number of DDDs of gabapentin increased from 0.35 in 2005 to 1.58 in 2008 and decreased to 0.04 in 2013. In contrast, the study in Norway (35) found gabapentin prescribing increased dramatically from 0.2 DDD per 1,000 persons in 2004 to 3.5 in 2013 among patients with neuropathic pain (Figure 2-a).

The number of patients prescribed pregabalin at least once increased to differing extents in the UK and Italy, while it fluctuated in USA (Figure 2-b). Studies in Australia (37) and Norway (35) both found the pregabalin DDD rates increased during their respective study periods. Three papers (8,33,44) reported the rate of patients who were prescribed pregabalin and they all found the rate increased in their respective study periods. However, the prevalence and incidence of pregabalin prescribing in Italy fluctuated (34) (Figure 2-b).

There are some obvious reasons why there were differences in these trends. Firstly,

the study population reported in these papers were different, such as general population, population with specific age ranges, population with specific diseases and populations who were prescribed at least one AED. Secondly, the variables used to quantify gabapentinoids prescribing also varied from study to study, including numbers of DDDs, prevalence, number of patients, the proportion of patients and incidence. Additionally, the time periods these papers reported also varied.

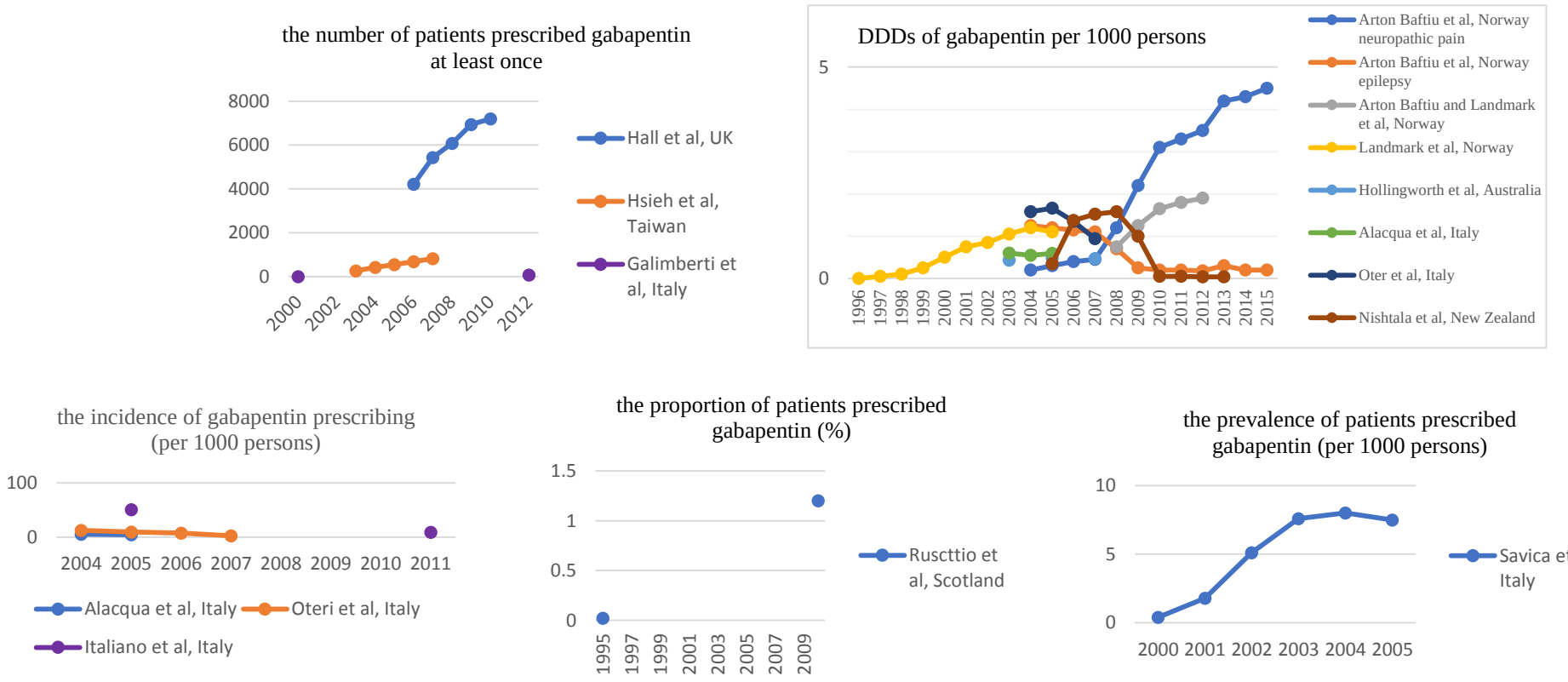

Figure 2-a. The rates and trends of gabapentin each year from different papers within the systematic review

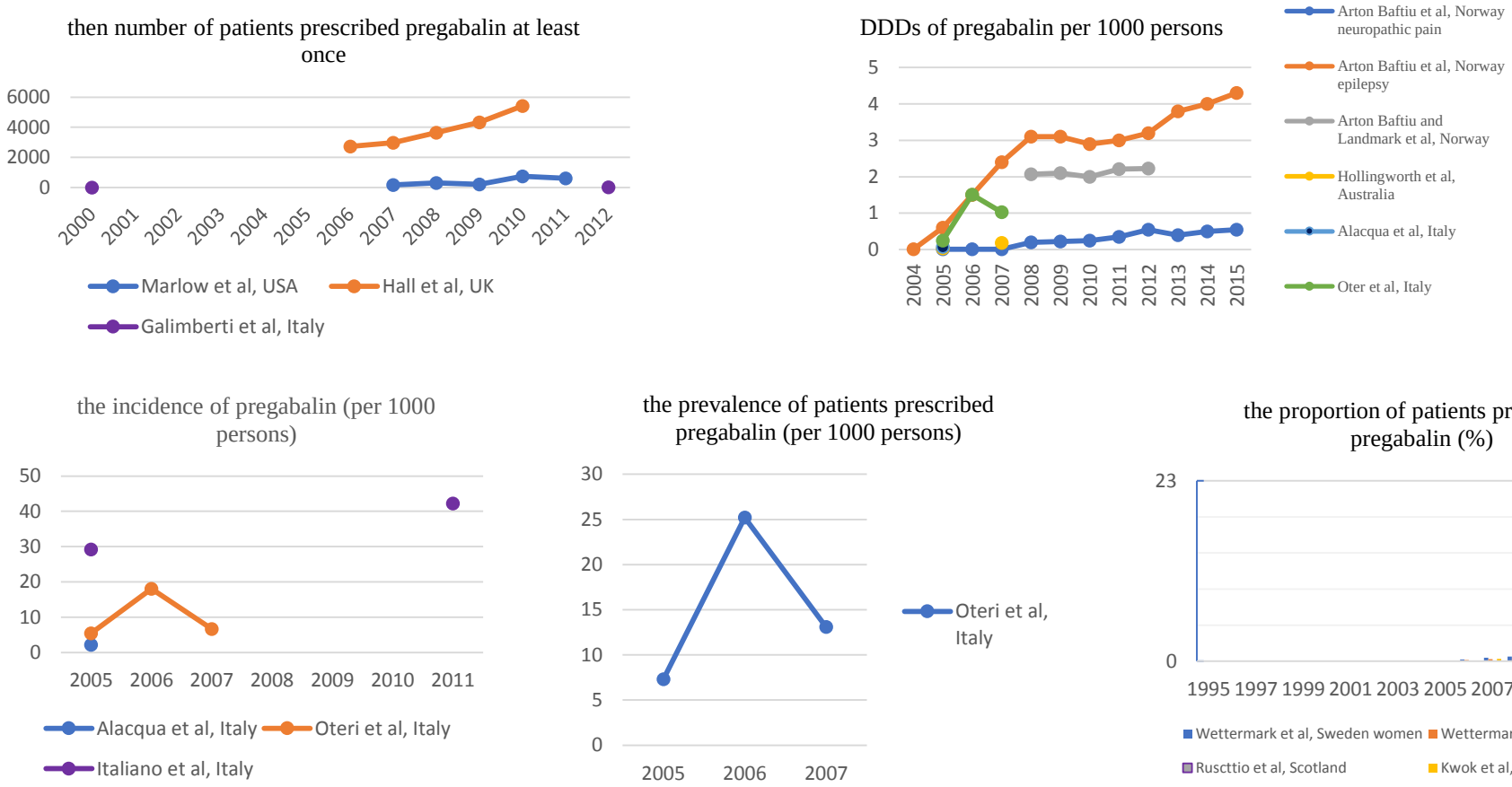

Figure 2-b. The rates and trends of pregabalin prescribing from different papers within the systematic review

There were three studies undertaken in Norway (35,38,41). Two papers included the numbers of DDDs of gabapentin prescribed from 2004 to 2006, although their study periods were nine years (41) and 12 years (35). The paper written by Landmark et al (41) reported that the number of DDDs of gabapentin increased from 0.8 in 2004 to 1 in 2005 and then decreased to 0.9 in 2006 (per 1,000 persons per day), while the paper written by Arton Baftiu et al (35) reported that the number of prescribed DDDs of gabapentin increased from 0.2 in 2004 to 0.4 in 2006 for neuropathic pain patients and decreased from 1.25 in 2004 to 1.15 in 2006 for epilepsy patients (per 1,000 persons per day). The difference is mainly due to the study population, one studying the whole population (41), the other studying people who were aged over 60 years old (35). Additionally, the study compared the number of prescribed DDDs of gabapentin among patients with neuropathic pain, epilepsy and psychiatry (35), while the other one calculated the number of prescribed DDDs of gabapentin among all patients prescribed gabapentin at least once (41). Landmark et al (41) reported the trends of gabapentin prescribing among the whole population in Norway from 1996 to 2014. However, there was one limitation to this paper in that the results were shown graphically as a line chart, making it difficult to calculate exact values for DDDs each year. The paper written by Baftiu and Landmark et al (38) reported that the number of prescribed DDDs of gabapentin increased from 0.75 per 1,000 persons in 2008 to 1.9 in 2012 in Norway. This paper studied all people in Norway and used the Norwegian prescription database, therefore the results could reflect the change in gabapentin prescribing in the Norwegian general population from 2008 to 2012, but it failed to give the exact values for DDDs each year.

Two studies (43,44) in Canada were both cross-sectional time series study. One written by Kwok (44) only reported the rate of pregabalin from 2006 to 2014 among all ODB-eligible individuals. This study found that there was a great increase in pregabalin use from 1 in the first quarter of 2013 to 22 in the last quarter of 2014 (per 1,000 persons), mainly because the policy on access to pregabalin changed from an authorization model to unrestricted model on April 1, 2013 in Canada. However, this

study failed to assess the use of medication paid for out of pocket or by private insurance, so maybe the rate of pregabalin use was underestimated. Additionally, the generalizability of the results in this study were restricted to the elderly with low socioeconomic status due to the database used, and the study population was eligible for public drug coverage. Thus, part of the observed pregabalin use increase may have resulted from the fact that some patients switched from private insurance to public drug coverage. The other paper written by Leong et al (43) compared the prevalence of gabapentin prescribing among non-epileptic patients and epileptic patients in Manitoba, Canada from 1998 to 2013. The most striking finding in this paper was that the gabapentin use increased dramatically among non-epileptic patients. It also found more than half of all AED users were using gabapentin in 2013. It was postulated that the observed rise in gabapentin use was due to the fact that gabapentin was widely used for neuropathic pain, and potentially also abused (49). In Canada, pregabalin was approved for neuropathic pain and fibromyalgia, but was not covered by public health plans (50). Thus, the restricted access to pregabalin may have also resulted in the rise of gabapentin use for pain conditions. This study is of high quality, so it can represent the prevalence of gabapentin prescribing in the general population in Manitoba, Canada during 1998 to 2013. A similar instance was noted by Hsieh et al in Taiwan (39) in that the proportion of patients prescribed gabapentin rose significantly among patients with neuropathic pain, while it was quite stable among epileptic patients. This study also found that the number of gabapentin prescriptions increased gradually amongst the older group aged 55 or older, probably because gabapentin was used for pain disorders and pain disorders are common among older people (51). However, this study only included patients who were prescribed at least two AEDs from 2003 to 2007, so the patients who only received one prescription were excluded. Thus, the exact number of gabapentin users each year was underestimated and the actual trends in the proportion of gabapentin prescribing may be a little different from that among a general population in Taiwan from 2003 to 2007.

There were five papers from Italy (31,32,34,36,42). As they studied different time

periods and different populations, in addition to various independent variables used, it is difficult to synthesize the results. However, it is interesting that one paper (32) reported that the incidence of gabapentin prescribing in 2011 was much lower than that in 2005 among each group of patients with epilepsy, pain and psychiatry in Caserta, Italy. Especially for patients with pain disorder, the incidence decreased almost 7-fold in 2011 (7.3 per 1,000 persons) compared with 2005 (47 per 1,000 persons). This study also found that the number of gabapentin prescriptions peaked in 2006 and then decreased from 2007, probably because of the endorsements of a health policy measure (Nota4) (26). From 2007, in Italy, all AEDs were reimbursed by the National Health Service for all indications, while gabapentin was only free for epilepsy or severe neuropathic pain from post-herpetic neuralgia, diabetic neuropathy or cancer (52). The most striking point the study (32) found was that the trends of gabapentin and pregabalin prescribing were mutually dependent. It seems that the decrease in gabapentin prescribing was balanced by the increase in pregabalin prescribing in the corresponding years, probably because gabapentin and pregabalin are made by the same company, prescribed for similar indications, and gabapentin use was influenced by the promotion strategy of pregabalin (53,54). This study is of high quality, though it only studied the population aged 15 years old or older. Another paper (34) also found the incidence of gabapentin prescribing decreased from 2004 to 2007 in Caserta. However, this study only selected patients aged 65 or over, using outpatient data, so the incidence of gabapentin prescribing may be underestimated. Thus, these results cannot be generalized to the general population in Italy.

Interestingly, one study in Sweden (8) found that pregabalin was dispensed more frequently to women than to men in Stockholm each year from 2006 to 2009, which was opposite to a Jordan study where 71.4% were males among the study population from November 2016 to January 2017 (55). However, the study in Jordan only included 77 patients requesting pregabalin and the study period was quite short.

In this systematic review, only five papers were of high quality (8,32,36,38,43). Other

studies had obvious limitations, so their results could not be generalized to the general population. The most common limitations of these included papers without high quality was the study population with specific age ranges, specific diseases, residence in nursing home or commencing gabapentin or pregabalin, which limited the relevance of these included papers to the research questions. The study in UK (46) only included the patients with a first gabapentin or pregabalin prescription during the study period, and did not include the patients who were already being prescribed gabapentinoids. Thus, the results are likely to be an underestimate compared with the actual number of patients who were prescribed gabapentin or pregabalin each year in the UK from 2006 to 2010. The paper from the USA (45) reported the trends of pregabalin prescribing, but the trends could not reflect the pregabalin prescribing trends in the general population in South Carolina, because this study included only a fibromyalgia cohort in which the pregabalin prescribing was likely to have been very different from a population with other diseases. Additionally, in this paper, the number of patients prescribed pregabalin was calculated from baseline characteristics, and therefore did not include the number of patients who were prescribed pregabalin during the follow up period. Five studies (34,35,40,42,44) were restricted to an elderly population and one study in Australia (37) had a lack of details about the study population. Thus, these papers could not reflect the trends of gabapentin or pregabalin in the general population.

Among the five papers of high quality, the study periods of four studies (8,32,36,38) were 2008-2012 (38), 2005-2011(32), 2005-2009 (8) and 2000-2005 (36), while one (43) studied gabapentinoids use from 1998 to 2013. However, this study (43) only studied pregabalin and calculated the prevalence of pregabalin prescribing among epileptic patients and non-epileptic patients separately, so it did not report the total prevalence of pregabalin prescribing among the population being studied. The results of this study were shown graphically by a line chart, so it failed to give the exact values for the prevalence of pregabalin. In addition, it did not study pregabalin use in the recent four years. Thus, a more comprehensive and detailed study of the changes in

gabapentin and pregabalin prescribing in recent years is required in the future.

Strengths and limitations

This systematic review has some strengths. Firstly, this study is the first systematic review of the rates and trends of gabapentin and pregabalin prescribing in a general population. Previous studies are either observational studies or reviews of gabapentin or pregabalin misuse. Thus, this study is the first one to summarise the current published evidence on gabapentinoids prescribing trends. Secondly, this study conducted quality assessments for each citation included in the review and analysed the strengths and limitations of these citations. The quality assessment tool was not an existing tool but modified from several quality assessment tools on observational studies. The quality assessment was also influenced by the other comments listed on the quality assessment table, making the assessment more comprehensive. Thirdly, this systematic review was conducted with a strict systematic approach. The selected databases were all authoritative and commonly used for searching medical papers or medicine related papers. The combination of these databases contains most published English language papers related to the study topic with reference list manual checking also conducted. The selection criteria were assessed and modified several times prior to use. The paper selection was conducted in strict accordance using the selection criteria by two independent reviewers, which was effective to reduce the selector bias. Finally, the search strategy used MeSH terms in combination with free text, which made the search more efficient and comprehensive.

However, the biggest limitation of this study is that this review only selected peer-reviewed studies, with grey literature being excluded, as it is difficult to extract and integrate data from grey literature due to the heterogeneity and it is also hard to assess the quality of grey literature (56). Another limitation was that after quality assessment, papers of low quality (37,41,42) were not excluded. The study population of some papers does not represent the general population, but they were also included in the review (34,35,40,42), because they also showed the trends of gabapentinoids in elder

people or patients with epilepsy which was relevant to our research question. However, this may reduce the power of the systematic review and make the results from these papers difficult to synthesize, but inclusion of these papers was due to a limited amount of published papers studying the trends of gabapentinoids prescribing in a large population. There was still a language bias, because we only can read English and Chinese. After searching the key databases, all papers were written in English, without any Chinese papers, while after paper selection, there was one paper from Taiwan (39) written by Chinese researchers but written in English. Finally, the heterogeneity in study characteristics and reporting made synthesis and direct comparisons difficult or impossible.

2.5. Conclusion

A comprehensive systematic review was conducted and 17 papers were included and underwent quality assessment. After the results from these papers were summarised, the trends of gabapentin and pregabalin prescribing rates varied between different countries. Because of the limitations of these papers, a further and more comprehensive epidemiological study focusing on the general population over a prolonged period is needed to identify the trends of gabapentin and pregabalin prescribing rates in a general population. Ideally, this should include data from the time that the gabapentin or pregabalin were introduced to market to the latest year. The aims of this epidemiological study should include identification of rates of gabapentinoids prescribing during these years, factors associated with gabapentinoids prescribing (clinical, socio-demographic, patient/professional), and outcomes (benefits and harms). This information could provide evidence for identifying the reasons for rising gabapentinoids prescribing, and the effects of this, so that the appropriate policy could be designed and implemented to rationalise gabapentinoids use.

3. Data analysis

3.1. From the systematic review to data analysis

The systematic review found that the trends of gabapentin and pregabalin prescribing differed in different countries. These papers within the systematic review did not study the same period or same years. The variables used to evaluate the gabapentin or pregabalin prescribing also varied from paper to paper, such as number of DDDs per 1,000 persons per year (31,34,35,37,38,40,41), prevalence (34,36,43), incidence (31,32,34), the number of patients (39,42,45,46) and the proportion of patients (8,33,44). Thus, the results of these papers could not be synthesized appropriately. Additionally, only five papers (8,32,36,38,43) within the review were of high quality. However, there were some limitations even to these five papers. Firstly, two papers (38,43) reported the trends by line and bar charts, failing to show the exact values. Secondly, the study periods of three papers (8,32,38) were 2008 – 2012, 2005 – 2011 and 2005- 2009 respectively. They did not summarise the change in trends of gabapentinoids use in recent years. The other paper written by Savica et al (36) only studied the prevalence of gabapentinoids prescribing from 2000 to 2005, failing to report the prevalence after 2005 and show the change of gabapentin prescribing after pregabalin was marketed in 2005. Thirdly, the paper by Leong et al (43) summarised the prevalence of gabapentin prescribing from 1998 to 2013, but it gave the change of prevalence among epileptic patients and non-epileptic patients separately, so it failed to summarise the prescribing trends for the whole population. Thus, there was a need to conduct a further study to summarise the trends of gabapentin and pregabalin prescribing in recent years among a general population.

In Scotland, there has been a significant increase in the number of gabapentin and pregabalin prescriptions, seen by summarising the prescribing data from the ISD website (57). However, there is no published evidence on the number of patients who were prescribed gabapentin or pregabalin each year in Scotland nor the total number of gabapentin and pregabalin prescriptions issued in each individual Health Board.

Additionally, the evidence on whether the gabapentinoids prescribing is associated with demographic factors and health outcomes, such as cancer, death, outpatient health service use, accident and emergency service use, is also limited.

In 2013, the number of deaths associated with pregabalin significantly increased from 2013 (19 deaths) to 2014 (38 deaths) in the UK (24). The number of deaths associated with gabapentin also climbed up from 17 in 2013 to 26 in 2014 (24). The number of death certificates in which gabapentinoids were cited significantly grew from less than 1 per year prior to 2009 to 137 in 2015 in England and Wales (26).

Thus, part two of this work would address the gaps found by the systematic review, aiming to summarise the prescribing rates and trends of gabapentinoids in Tayside over 11 years (2006-2016) and Fife over seven years (2010-2016) and investigate their associations with demographic factors and the use of health services. This study would be the first one to investigate gabapentinoids prescribing rates in Tayside and Fife over recent years. It aims to provide epidemiological evidence on the patterns of gabapentin and pregabalin prescribing to allow policy makers (such as NHS Tayside and the Scottish Government) to make fitting policy changes to make the prescribing of these drugs more appropriate. Additionally, it is hoped this study will provide useful evidence for further studies.

3.2. Methods

3.2.1. Ethics and permission

The data for this study were provided by the “Safe Haven” platform from the Health Informatics Centre (HIC) at the University of Dundee. The current version of the HIC Data User Declaration (DUD) was signed and the MRC E-course 'Research Data and Confidentiality' was completed by the author and supervisors.

The server “Safe Haven” is used to protect data confidentiality, providing a restricted and secure IT environment. In such an environment, users cannot export data out of the server to their own computer for analysis but receive secure access to data and

statistics software and undertake analysis on the server. Results cannot be released externally without approval of HIC administrators.

3.2.2. Data management

3.2.2.1. Data source

The large dataset and data-linkage for this study were prepared by HIC, including datasets of routine health and administrative data, reporting: prescriptions, demography, cancer registrations, death registrations, Accident and Emergency attendances (A&E), and hospital admissions.

The prescribing dataset consists of gabapentin or pregabalin prescriptions in Tayside from 2006 to 2016 and Fife from 2010 to 2016. It contains the details of each prescription dispensed, recording the prescribed date, the drug name, the strength, the quantity of drug dispensed, the instruction for taking prescribed medicine, the unique number of the drug, and the health board. The medicines, gabapentin and pregabalin, are identified by the British National Formula (BNF) code of 4.8.1.

The demography file consists of 63,253 single records coming from the national CHI dataset, recording the demographic details for patients in Tayside and Fife health boards. This is based on the Community Health Index (CHI), which attributes a unique number to every individual who is registered with the NHS in Scotland. The demographic factors include gender, age (= 2017-the year patient was born), Health Board area of NHS registration, rurality and the Scottish Index of Multiple Deprivation (SIMD). SIMD is classified into five quintiles to reflect the socioeconomic level and SIMD1 represents the most deprived quintile. Rurality with six groups was recorded in accordance with the Scottish Government 6-fold Urban Rural Classification: large urban, other urban areas, accessible small towns, remote small towns, accessible rural and remote rural.

The death dataset includes all deaths registered in all Health Boards areas in Scotland from 2007 to 2017, with the underlying cause of death coded by the International

Classification of Diseases, 10th edition (ICD-10). The cancer registration dataset records all incidences of cancer registered in 2016 in Tayside and Fife Health Boards. The hospital admissions datasets, A&E dataset and outpatient dataset only contain attendances that occurred in 2016 in all Health Boards of Scotland.

The Data-linkage focuses on data recorded in 2015 and 2016 (Figure 3). All the datasets were linked by matching the Pro-CHI of the patient. The Community Health Index (CHI) is used as a unique personal identifier allocated for each patient on first registration with GP practices in Scotland. Pro-CHI is an anonymized number for CHI created by the HIC analysts to protect personal information.

The number of gabapentin and pregabalin prescriptions in Scotland and the total number of people in Tayside, Fife and Scotland originated from Information Services Division (ISD) and National Records of Scotland (NRS) websites.

Figure 3. Overview of gabapentinoids prescribing data linkage for NHS Fife & Tayside in 2015 and 2016

3.2.2.2. Data cleaning and grouping

GP Prescribing dataset (Tayside 2006-2016, Fife 2010-2016)

Excel was used to manage this dataset. First, the dataset was cleaned by removing the duplicate cases. Duplications were defined as cases that were the same in all of seven variables, ProCHI, Corrected prescribing date, Res-seqn which is the drug identifier, quantity, drug name, strength, and health board. Second, according to the corrected prescribed date, the prescriptions of gabapentin and pregabalin in the same year were selected into tables. As the data were not presented as expected, organized as a form of each prescription with Pro-CHI, and several rows referring to different dates for one patient, a pivot table was used to summarise the counts of prescriptions for each patient every year. Thus, by using the pivot tables, the reconfigured dataset presents a single record for each patient and the record contains the counts of gabapentin and pregabalin prescriptions per year for each patient, called Dataset 1 which would be used to summarise the trends of gabapentin and pregabalin prescribing from 2006 to 2016. For 2015 and 2016 data the pivot tables were merged into one dataset with the cases missing Pro-CHI being deleted. The merged dataset had five new variables created: patients prescribed gabapentin or pregabalin in 2015; patients prescribed gabapentin or pregabalin in 2016; patients prescribed gabapentin or pregabalin in both years; patients prescribed both pregabalin and gabapentin in 2015; and patients prescribed both pregabalin and gabapentin in 2016. This merged dataset was called Dataset 2 which would be used to link the other demographic and health outcome datasets.

For the other six datasets being linked, firstly, the duplications were checked and removed for each, then each dataset was managed as described below.

Demography file

The demographic file reports age as a continuous variable calculated until the end of 2017. This variable was re-categorized into five age groups: 0-17, 18-40, 41-60, 61-80 and 80+ years. Because people aged under 18 and over 80 were both specific age

groups, children and the extreme elderly, 0-17 and 80+ became two independent groups. People aged between 18 and 80 were divided into three groups with a 20-year interval.

SMR06 Cancer register

Pivot tables were used to summarise the episodes of cancer for each patient. The patients were categorized into two groups: without cancer episode, and with at least one cancer episode.

GRO Death dataset

The underlying cause of death was presented as ICD-10 codes by HIC for applicable patients. This study grouped the underlying cause of death coded by ICD-10 as follows.

1. Disease of circulatory system (I00-I99)

    1.1 Acute myocardial infarction (I21, I22, I23)

    1.2 Ischaemic heart disease including angina (I20, I24, I25)

    1.3 Cerebrovascular disease (I60-I69)

2. All neoplasm (C00-D48)

    2.1 Neoplasms of the digestive organs (C15-C26)

    2.2 Neoplasms of the respiratory and intrathoracic organs (C30-C39)

3. Disease of respiratory system (J00-J99)

    3.1 Pneumonia (J12-J18)

    3.2 Chronic lower respiratory disease (J40-J47)

4. Disease of digestive system (K00-K93)

5. Disease of the nervous system (G00-G99)

6. All other causes

SMR01 Hospital admissions dataset

Pivot table function was used to summarise the counts of attendance, average length of hospital stay, as well as minimum and maximum length of stay for each patient.

Accident & Emergency dataset

Pivot table was used to summarise the counts of attendance for each patient.

SMR00 Outpatient appointment

Pivot table was used to summarise the counts of appointments for each patient according to the clinical date of attendance.

3.2.2.3. Data linkage

Dataset 2 was linked with all other cleaned and grouped datasets by matching Pro-CHI in Excel using the VLOOKUP function. VLOOKUP is a built-in function in excel to lookup and retrieve data from a specific column in a table and it supports approximate and exact matching. Lookup values must appear in the first column of the table, with lookup columns to the right.

=VLOOKUP (Value you want to look up, range where you want to lookup the value, the column number in the range containing the return value, Exact Match or Approximate Match – indicated as 0/FALSE or 1/TRUE)

3.2.3. Data analysis

3.2.3.1. Descriptive analysis

The frequencies of gabapentin prescriptions, pregabalin prescriptions, patients who were prescribed at least one gabapentin and patients who were prescribed at least one pregabalin in each year in each health board, Tayside and Fife, were summarised. In one day, for the same patient, the prescriptions of the same medicine would be counted as different prescriptions if they are different in one of the variables strength, quantity

and res-seqno which is the drug identifier. To specifically evaluate the trends of gabapentin and pregabalin prescribing in Tayside, Fife and Scotland, six calculations were conducted as follows.

1. The number of patients who received at least one gabapentin prescription each year in Tayside (2006 to 2016) and Fife (2010 to 2016) separately.
2. The number of patients who received at least one pregabalin prescription each year in Tayside (2006 to 2016) and Fife (2010 to 2016) separately.
3. The total number of gabapentin prescriptions each year in Tayside (2006 to 2016) and Fife (2010 to 2016) separately.
4. The total number of pregabalin prescriptions each year in Tayside (2006 to 2016) and Fife (2010 to 2016) separately.
5. The gabapentin or pregabalin prescribing rate is calculated as (No.1 or No.2*100) divided by the total population in corresponding health board per year, with the unit (%).
6. The average number of gabapentin or pregabalin prescriptions per 1,000 persons is calculated as (No.4 or No.5 *1,000) divided by the total population in corresponding health board per year.

The data in relation to the number of gabapentin and pregabalin prescriptions in Scotland each year from 2006 to 2016 was collected from the Information Services Division (ISD) website (57) and the total of the Scottish population for each of these years was gathered from available data on the National Record of Scotland (NRS) website (58). This allowed the average number of gabapentin and pregabalin prescriptions per 1,000 persons in Scotland to be calculated, which could then be compared with the figures in Tayside and Fife.

SPSS version 22 statistical software programme was used to summarise the characteristics of gabapentin and pregabalin prescribing in each of the two years, 2015

and 2016 in relation to demographic factors: gender, age, SIMD, rurality and Health Board. Descriptive analyses for cancer, death, underlying cause of death, outpatient appointments, hospital admissions and A&E were also conducted. Population pyramid figures were used to describe the distribution patterns of the total counts of gabapentin and pregabalin prescriptions each individual person received in both Tayside and Fife per year in 2015 and 2016, and potential differences between female and male patients were also calculated.

3.2.3.2. Age standardisation

Age standardisation can allow for the difference of age structures of populations and age standardised mortality can make the mortalities directly comparable in different populations which are different in age structure. To compare the age standardised mortality of the gabapentinoids prescribing population with Scottish national age standardised mortality data from the NRS website, the age of this study population was re-categorised into 19 groups to match the NRS categories with a 5-year interval, such as 0-4, 5-9, 10-14 up to 90+. The underlying cause of death was divided into three groups, circulatory deaths, respiratory deaths and all other deaths to match the NRS categories. The frequency of patients who were prescribed at least one gabapentinoid in 2015 and 2016 in each age group were summarised. In this study population, the counts of deaths in each age group in 2015 and 2016 were also summarised.

The standard population used was the 2013 European Standard Population (ESP) and this was applied to the Scottish national age standardised mortality calculation in 2015 and 2016. The formula provided from the Office for National Statistics was used to calculate the age standardised mortality of this study population.

$$\text{Age standardised Mortality} = \sum(p_k\, m_k) / \sum p_k$$

p_k = the number of people of the standard population in age group (ESP)

m_k = observed mortality rate (per 100,000) in age group

k = age group

The age standardised mortality in this study was an average standardised death rate for two years, 2015 and 2016. The average Scotland standardised mortality for 2015 and 2016 was equal to the mean of the Scottish standardised mortalities in 2015 and 2016. The age standardised mortality rate was calculated for each of the underlying causes of death and the total number of deaths. Relative risk and 95% confidence intervals were calculated for each age standardised mortality rate by OpenEpi, version 3.01. OpenEpi is a free, web-based and open source software for use in epidemiologic statistics.

3.2.3.3. Regression

This study used two types of regression model to examine the association of gabapentinoids prescribing and demographic factors. The first is a logistic regression model used to investigate what demographic factors were likely to be associated with the prescribing of gabapentin or pregabalin. The second is the Poisson model used to examine which demographic factors would be associated with an increase in the number of gabapentin or pregabalin prescriptions among patients who had already been prescribed gabapentin or pregabalin at least once.

Logistic regression model

Logistic regression modelling is used to test the association between a binary outcome and one or more factors. In this study, the population studied by the logistic regression model was patients who had been prescribed only gabapentin or only pregabalin each year, so these patients who had been prescribed both gabapentin and pregabalin in the same year would not be analysed by the logistic regression model. In the model, prescribed pregabalin is the positive outcome and prescribed gabapentin is the negative outcome, and logistic regression modelling was fitted to evaluate the association between the outcome and the demographic factors of interest in each year, 2015 and 2016. The demographic factors included age group, SIMD, gender, health board and rurality. All of these factors were fitted into the logistic regression model as

categorical variables with the reference category being defined as the group with largest numbers; age 41-60; female; Tayside; and other urban groups were set as reference categories. SIMD1 represents the most deprived areas, so it was chosen as the reference category. The significance level was set as 0.05 ($\alpha = 0.05$) which means there was a 5% risk to reject the null hypothesis when it was actually true. The enter tool was used in each model, because this study was not to produce a prediction model but just to examine the associations. Thus, the factors which were not significant would also be kept in the model. The fitted logistic regression model is shown as follows;

$$Prescribed \sim Age + Gender + SIMD + Rurality\ group + Health\ board$$

Prescribed indicates that pregabalin were prescribed and gabapentin was not prescribed.

The odds ratio and 95% confidence interval were calculated by SPSS.

Poisson regression model

In statistics, Poisson regression is a generalized linear model to count data and construct contingency tables. In this study, the population studied by the model was patients who received at least one gabapentin or pregabalin each year. The Poisson model was used to test the association between demographic factors and the count outcome: counts of gabapentin or pregabalin prescriptions per patient. The independent demographic factors were age as a continuous factor, with gender, SIMD, rurality and Health Board entered as categorical factors. The significance level was set as 0.05 ($\alpha = 0.05$) which means there was a 5% risk to reject the null hypothesis when it was actually true. The Poisson model is constructed as below;

$$Log\ (counts\ of\ gabapentin\ or\ pregabalin\ prescription) \sim Age + Gender + SIMD + Health\ board + Rurality$$

The coefficient of each subgroup of each factor is called estimated effect size which is related to relative risk (RR);

eg. For gender, if female is the reference category, the coefficient of the male is X,

then RR= exp (estimated effect size of male) = exp (X)

exp(X) means if all the other covariates remain the same, the number of gabapentin or pregabalin prescribed in male group will be *exp (X)* times of that prescribed to reference category, female. (*exp (X)-1) *1000* means (*exp (X)-1) *1000* more prescriptions of gabapentin or pregabalin in 1000 male patients than 1000 female patients.

The reference category is the group with largest size. Each model would keep all of these five independent factors, including significant and insignificant factors, because the model was not used for prediction, but for evaluation of association between variables.

3.3. Results

3.3.1. Data cleaning

In the original prescribing dataset with 1,091,199 prescription records, 15,984 duplications were identified and removed (Figure 4). These pairs of duplicate cases had the same in Pro-CHI, drug identifier, strength, quantity, corrected prescribing date, drug name and health board. There were 1,075,215 prescription records remaining,and these related to 57,842 patients (Figure 4).

The prescription records in the same year were selected into the same table according to corrected prescribing date. In 2015, the prescribing table included 26,740 patients, 61,658 pregabalin prescriptions and 114,023 gabapentin prescriptions. In 2016, the prescribing table included 29,233 patients, 73,791 pregabalin prescriptions and 122,713 gabapentin prescriptions. The two tables were merged into Dataset 2 to include a single entry for each individual patient, with 36,800 patients after deleting 214 patients without Pro-CHI (Figure 5).

There were 63,235 patients with information on Pro-CHI, gender, SIMD, Health board, rurality, date of birth, age (ended in 2017) and postcode in the demography file and no duplications were found. The GRO death file contained 8,570 patients with an underlying cause of death coded with ICD-10. The SMR06 Cancer register dataset contained 733 records and 721 patients after 47 duplications were identified and removed. For the Hospital admission dataset, there were 42,287 records and 14,930 patients. The outpatient dataset contained 164,587 records and 36,852 patients after removing 1,293 duplications which were duplicated in Pro-CHI, specialty, location and clinic date (Figure 5).

These seven datasets were merged into one new dataset, Dataset 3, matched with Pro-CHI. There were 36,800 patients in Dataset 3 (Figure 5).

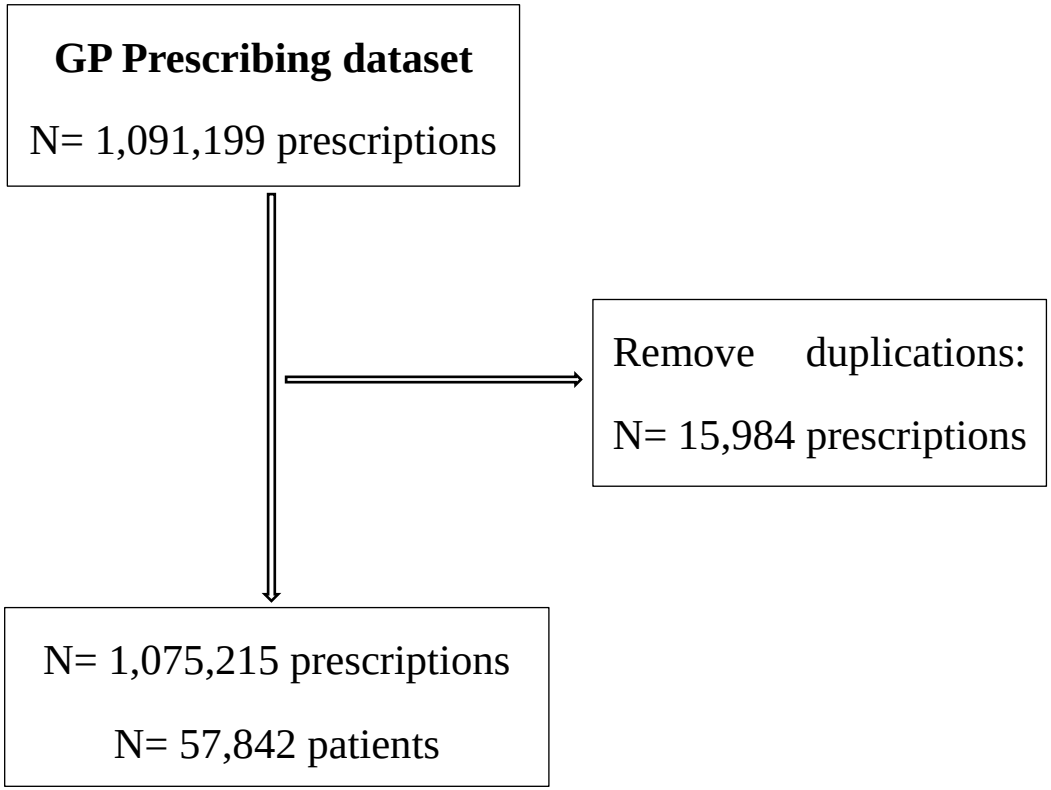

Figure 4. Flow chart of data cleaning for GP prescribing dataset

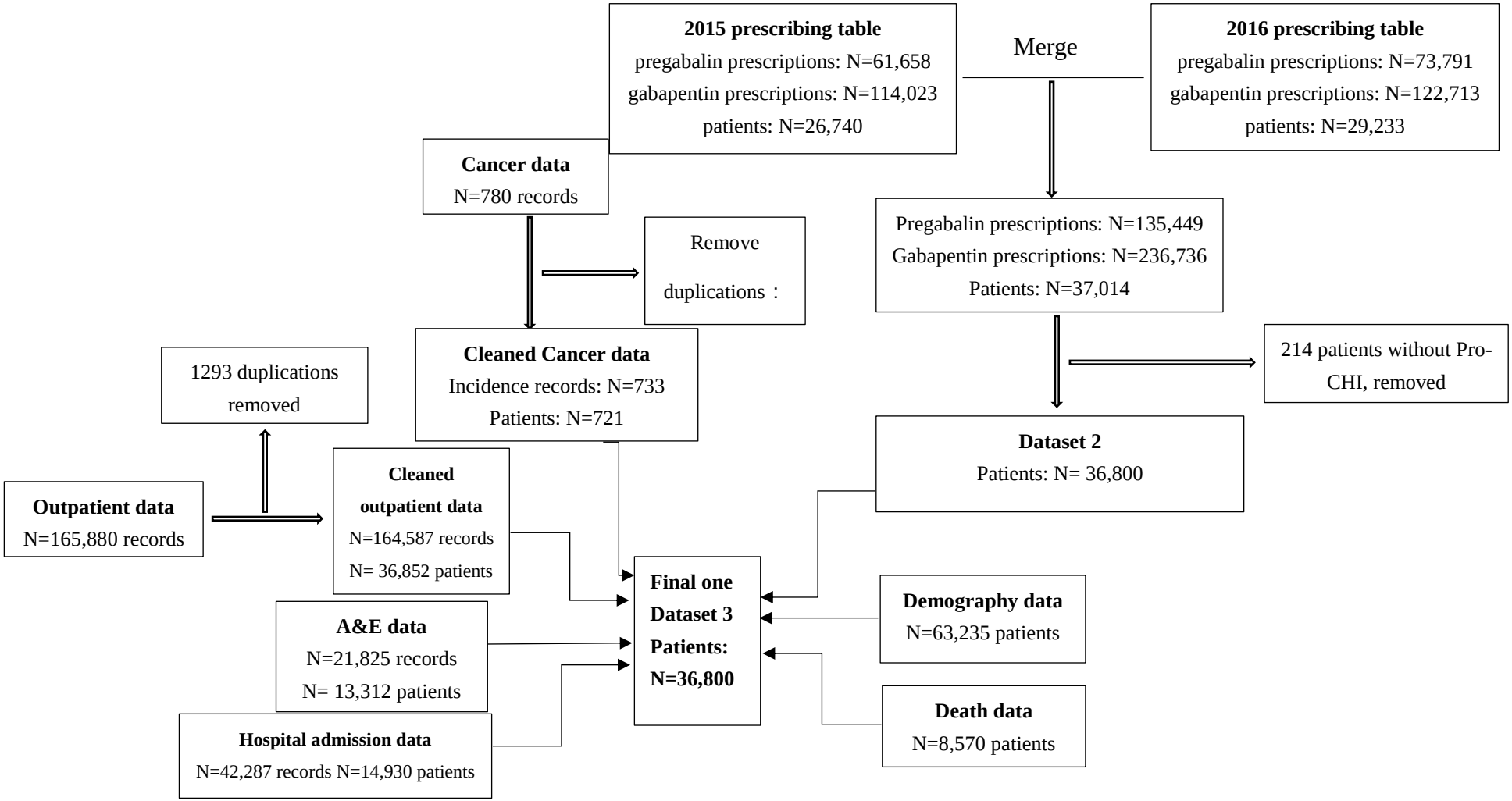

Figure 5. Flow chart of data cleaning for prescribing data and data linkage in Tayside and Fife in 2015 and 2016

3.3.2. Descriptive analysis

Cleaned GP Prescribing dataset

The prescribing trends of gabapentin and pregabalin in Tayside, Fife and Scotland were specified as the changing number of prescriptions, number of patients, the proportions of patients and the average number of prescriptions per 1000 persons for gabapentin and pregabalin respectively.

In Scotland, the number of gabapentin prescriptions increased gradually from 2006 to 2010 and then decreased slightly in 2011 and rose rapidly every year from 2012 to 2016. There were 694,293 gabapentin prescriptions in 2016 which was four times more than the 164,630 prescriptions in 2006. In Tayside, the number of gabapentin prescriptions grew gradually from 16,481 in 2006 to 31,615 in 2010 and then decreased slightly in 2011 to 29,519 and increased again from 2011 to 2016 to 57,472. In Fife, the number of gabapentin prescriptions increased gradually from 20,645 in 2010 to 65,241 in 2016 (Figure 6).

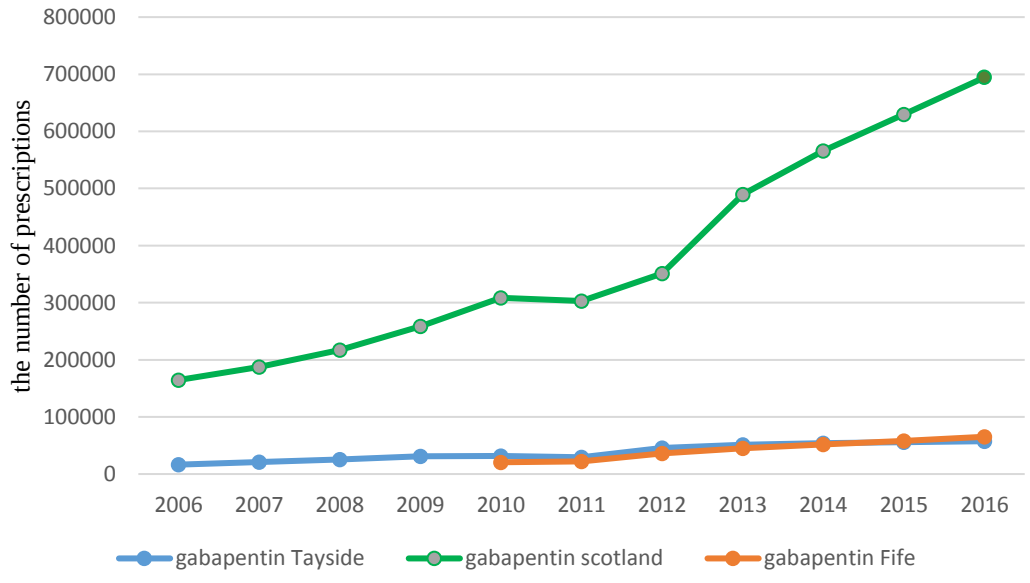

Figure 6. The number of gabapentin prescriptions in Tayside, Fife and Scotland from 2006 to 2016

In Scotland, the number of pregabalin prescriptions dramatically climbed up from 2006 (27,094) to 2016 (435,498, which is 16 times that of the figure in 2006). In Tayside, the number of pregabalin prescriptions increased sharply from 2006 to 2016; the figures in 2016, 48,648, are approximately 21.5 times higher than that in 2006 (2,271). In Fife, there was a gradual growth from 10,506 in 2010 to 25,143 in 2016 (Figure 7).

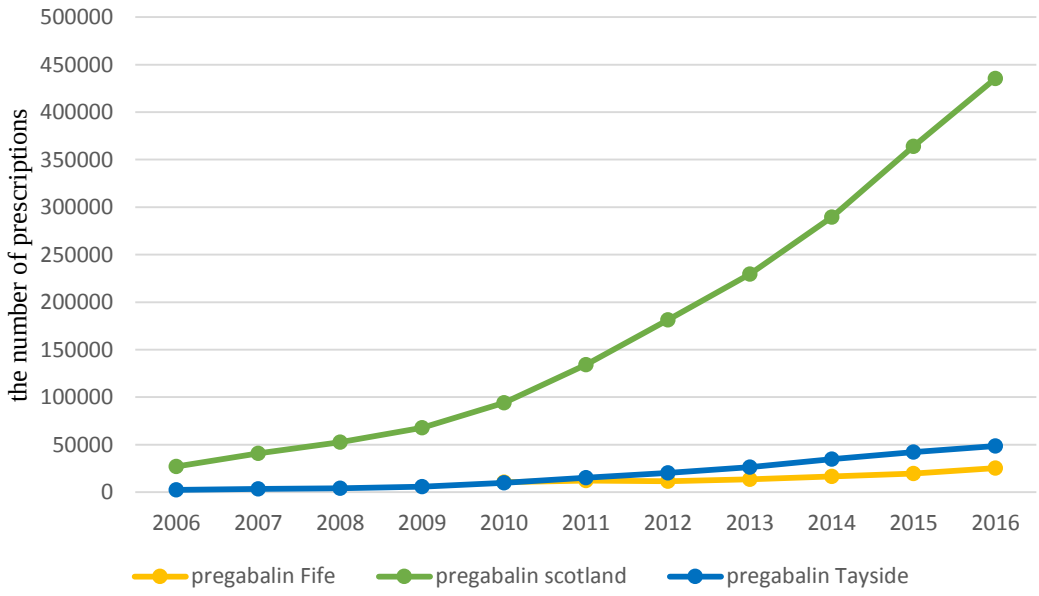

Figure 7. The number of pregabalin prescriptions in Tayside, Fife and Scotland from 2006 to 2016

The average number of gabapentin prescriptions per 1,000 persons in Scotland was lower than that in Tayside or Fife in the corresponding years: for Fife, the average number of gabapentin prescriptions rose dramatically from 2010 (57/1,000) to 2016 (176/1,000), an almost three-fold increase (Figure 8).

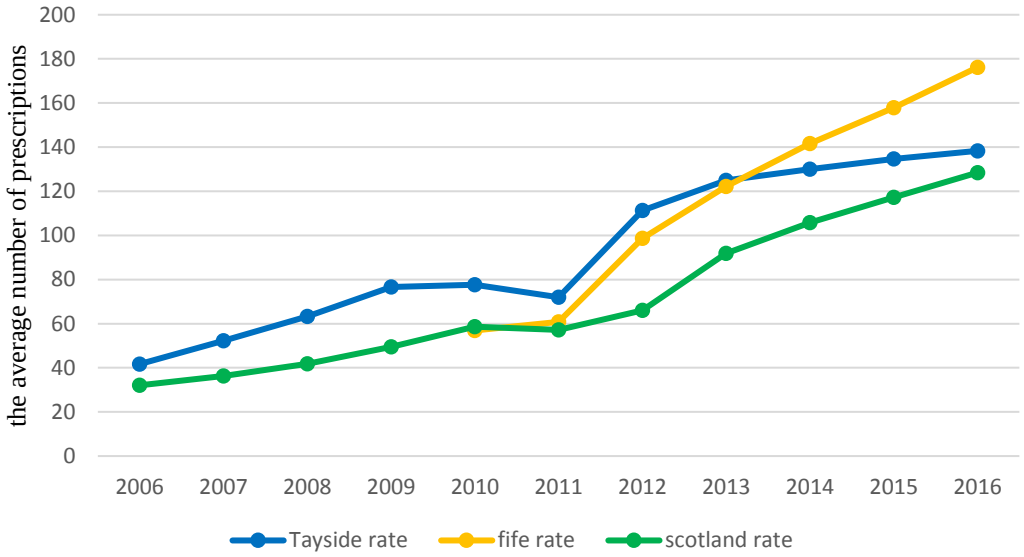

Figure 8. The average number of gabapentin prescriptions per 1000 persons in Tayside, Fife and Scotland from 2006 to 2016

Pregabalin prescribing in Fife was lower than that in Tayside and Scotland before 2012. Pregabalin prescriptions increased gradually in Tayside and Scotland from 2006 to 2010 and soared from 2010 to 2016. In 2016 in Tayside (117/1,000), it was almost 20 times higher than that in 2006 (6/1,000) (Figure 9).

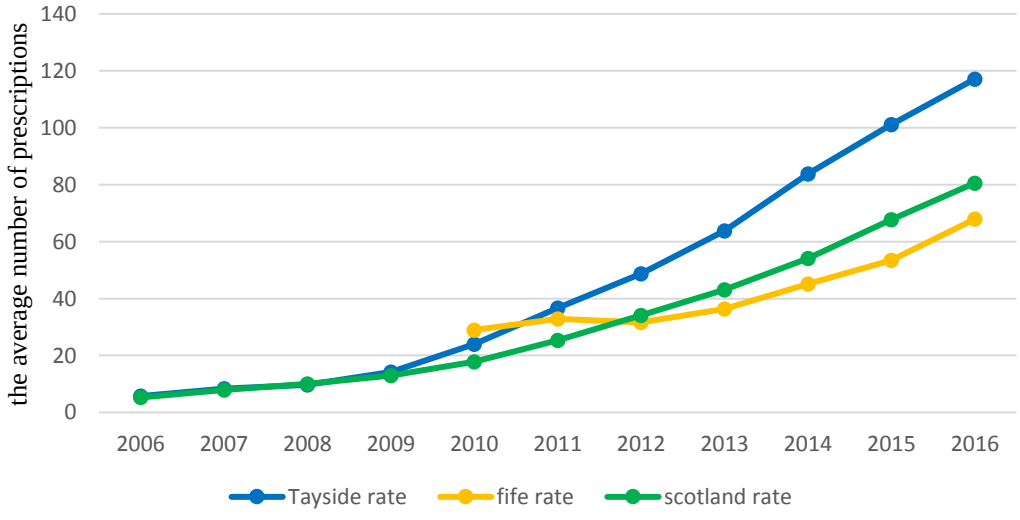

Figure 9. The average number of pregabalin prescriptions per 1000 persons in Tayside, Fife and Scotland from 2006 to 2016

The number of patients receiving at least one gabapentin prescription increased in Tayside and Fife, with a four-fold increase during the 11 years in Tayside (Figure 10). While for pregabalin, the number of patients decreased very slightly in Fife in 2012 before rising, for Tayside with the number of patients almost 15 times higher in 2016 (6,564 patients) than that in 2006 (442 patients) (Figure 11).

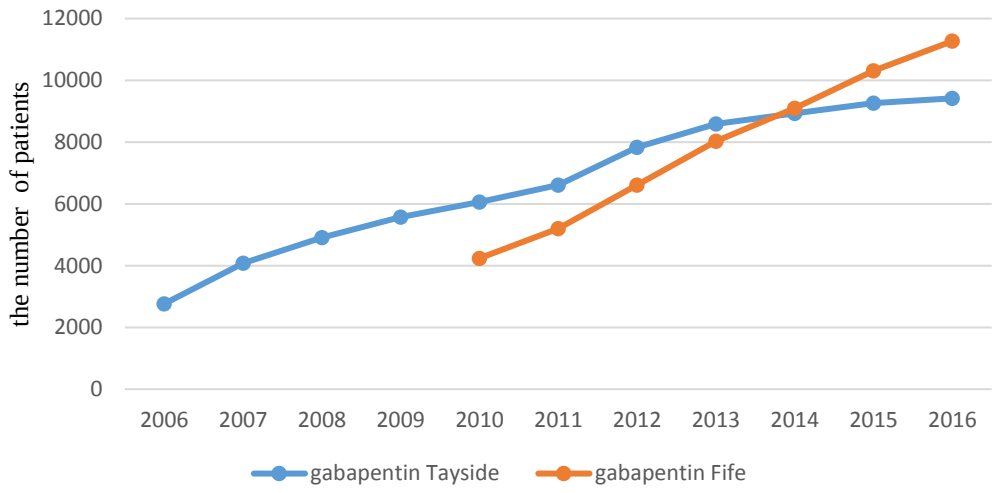

Figure 10. The total number of patients who were prescribed gabapentin at least once in Tayside and Fife from 2006 to 2016

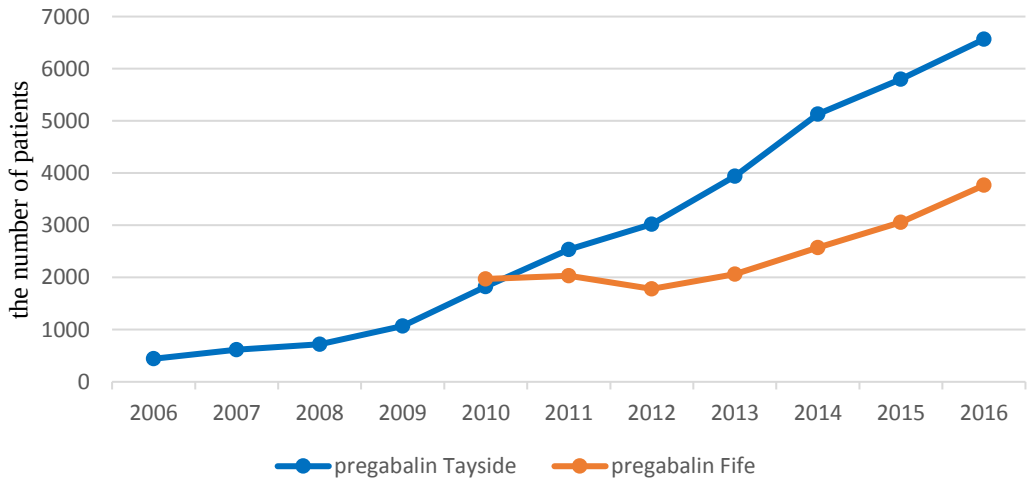

Figure 11. The total number of patients who were prescribed pregabalin at least once in Tayside and Fife from 2006 to 2016

The number of patients who were prescribed gabapentin at least once in Tayside

represents 0.7% to 2.27% of the total population in Tayside between 2006 to 2016 and 1.47% to 3.04% of the total population in Fife between 2010 and 2016 (Figure 12). For pregabalin, the rate increased from 0.11% in 2006 to 1.58% in 2016 in Tayside and the rate ranged from 0.54% to 1.02% in Fife between 2010 and 2016. (Figure 13)

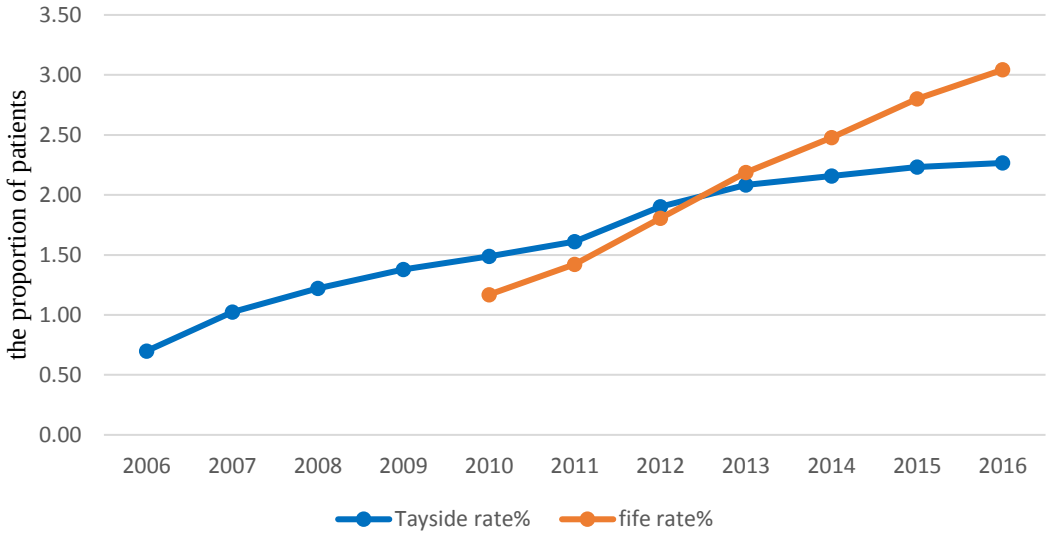

Figure 12. The proportion of patients who were prescribed gabapentin at least once in the total population of Tayside and Fife from 2006 to 2016

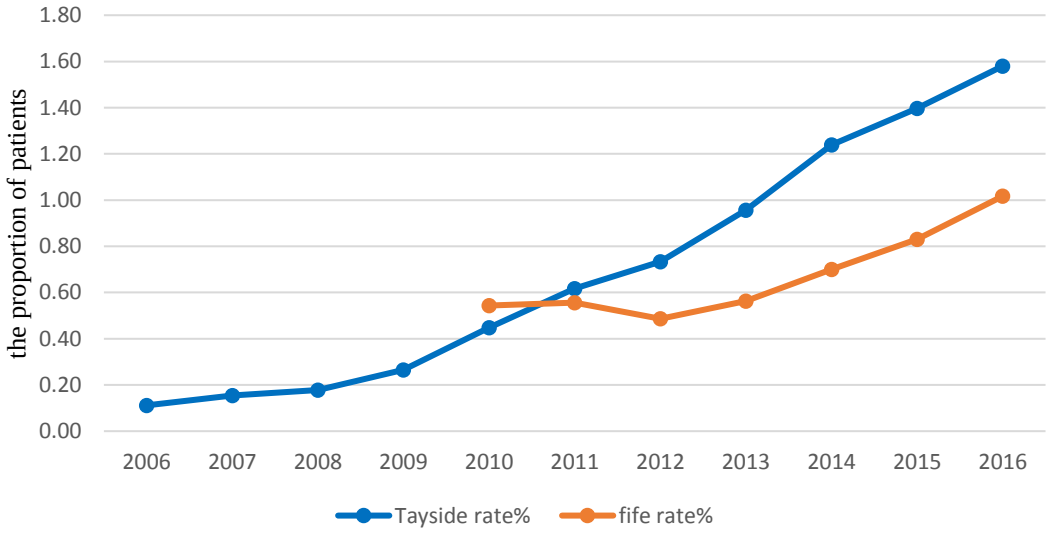

Figure 13. The proportion of patients who were prescribed pregabalin at least once in the total population of Tayside and Fife from 2006 to 2016

A total of 36,800 patients were prescribed gabapentinoids at least once in Tayside and Fife in 2015 and 2016. Of these, 26,637 patients were recorded in 2015 and 29,122 patients in 2016, with 18,959 patients prescribed gabapentinoids in both 2015 and 2016. The mean age of all patients prescribed a gabapentinoid during 2015 and 2016 was 58.19 (SD 16.15) (Table 5). Overall, only 46 patients (0.1%) were 17 years old or below and most patients (40.5%) were in the age group 41-60 years old; 62.4% of patients were female; and 53.6% of patients were resident in Tayside (Table 5). SIMD1 represents the most deprived quintile and SIMD5 is the least deprived quintile. The range of the proportion of patients amongst the five SIMD categories in 2015 and 2016 was 12.1% to 22.9% (Table 5). There were 16,324 patients (44.4%) resident in other urban area according to rurality code and 620 patients (1.7%) resident in a remote rural area in both 2015 and 2016 (Table 5). In 2015, a total of 26,637 patients were prescribed a gabapentinoid at least once; of them, 17,814 patients (66.9%) were only prescribed gabapentin and 7,139 patients (26.3%) were only prescribed pregabalin (Table 5). In 2016, a total of 29,122 patients were prescribed gabapentinoids at least once; 18,842 patients (64.7%) were only prescribed gabapentin and 8,503 patients (29.2%) were only prescribed pregabalin (Table 5).

Table 5. The demographic characteristics of patients who received at least one gabapentinoid in 2015 and 2016

	2015 (n=26,637)	*2016 (n=29,122)*	*Both 2015 and 2016 (n=18,959)*	*Total (n=36,800)*
Age (mean, SD)	58.73 (15.80)	57.95 (15.96)	58.58 (15.35)	58.19 (16.15)
Age group				
0-17	26 (0.1%)	34 (0.1%)	14 (0.1%)	46 (0.1%)
18-40	3,555 (13.3%)	4,296 (14.8%)	2,380 (12.6%)	5,471 (14.9%)
41-60	10,970 (41.2%)	12,110 (41.6%)	8,176 (43.1%)	14,904 (40.5%)
61-80	9,621 (36.1%)	10,158 (34.9%)	6,736 (35.5%)	13,043 (35.4%)
80+	2,465 (9.3%)	2,524 (8.7%)	1,653 (8.7%)	3,336 (9.1%)
Gender				
Female	16,626 (62.4%)	18,238 (62.6%)	11,874 (62.6%)	22,990 (62.4%)
Male	10,011 (37.6%)	10,884 (37.4%)	7,085 (37.4%)	13,810 (37.5%)
Health board				
Tayside	14,077 (52.9%)	15,029 (51.6%)	9,989 (52.7%)	19,117 (53.6%)
Fife	12,560 (47.1%)	14,093 (48.4%)	8,970 (47.3%)	17,683 (46.4%)
Scottish SIMD				
SIMD1	6,311 (23.7%)	6,911 (23.7%)	4,789 (25.3%)	8,433 (22.9%)
SIMD2	5,780 (21.7%)	6,347 (21.8%)	4,282 (22.6%)	7,845 (20.3%)
SIMD3	4,921 (18.5%)	5,441 (18.7%)	3,437 (18.1%)	6,925 (18.8%)
SIMD4	5,426 (20.4%)	5,893 (20.2%)	3,708 (19.6%)	7,611 (20.7%)
SIMD5	3,161 (11.9%)	3,329 (11.4%)	2,025 (10.7%)	4,465 (12.1%)
Rurality code				
Large urban	6,129 (23.0%)	6,418 (22.0%)	4,468 (23.6%)	8,079 (22.0%)
Other urban	11,752 (44.1%)	13,042 (44.8%)	8,470 (44.7%)	16,324 (44.4%)
Accessible small town	2,854 (10.7%)	3,123 (10.7%)	1,962 (10.3%)	4,015 (10.9%)
Remote small town	455 (1.7%)	507 (1.7%)	309 (1.6%)	653 (1.8%)
Accessible rural	3,976 (14.9%)	4,366 (15.0%)	2,754 (14.5%)	5,588 (15.2%)
Remote rural	433 (1.6%)	465 (1.6%)	278 (1.5%)	620 (1.7%)
Only gabapentin (number of patients)	17,814 (66.9%)	18,842 (64.7%)		
Only pregabalin (number of patients)	7,139 (26.8%)	8,503 (29.2%)		
Both prescribed (number of patients)	1,683 (6.3%)	1,777 (6.1%)		

A total of 19,498 patients in 2015 and 20,619 patients in 2016 were prescribed gabapentin in Tayside and Fife, including patients who were prescribed both pregabalin and gabapentin in the same year. The mean age of patients was 59.01 and 58.31 in 2015 and 2016 respectively; most patients were in the 41-60 years group (40.5% in 2015 and 40.7% in 2016); 23 patients and 1,826 patients respectively were below 18 years old and over 80 years old in 2015, while for 2016, 29 patients and 1,799 patients were respectively reported for these age groups (Table 6). Female patients were prescribed gabapentin more frequently than males, 62.1% and 62.4% in 2015 and 2016 respectively; most patients were from Fife (52.5% in 2015 and 54.4% in 2016) (Table 6). The smallest proportion of patients lived in SIMD5 in 2015 (11.7%), and the same with 2016 (11.4%) (Table 6). The largest proportion of patients lived in Other urban area in 2015 and 2016 (46.9% and 47.7% respectively), while the smallest proportion lived in remote small towns (1.5% in 2015 and 1.4% in 2016) (Table 6). There were 1,684 patients prescribed both gabapentin and pregabalin in 2015 and 1,777 patients prescribed both gabapentin and pregabalin in 2016.

In 2015, the average number of gabapentin prescriptions per person was 5.83, and the range was 1 to 36; the median was 5 (Table 6). The number of gabapentin prescriptions per patient per year in 2015 was not normally distributed (Figure 14). Most patients received more than one prescription of gabapentin but the number of patients who received one prescription was largest in 2015 whether they were female or male patients (Figure 14). The distribution pattern of the number of gabapentin prescriptions among male and female patients in 2016 was quite similar to that in 2015 (Table 6, Figure14-15).

Table 6. The demographic characteristics of patients who received at least one gabapentin prescription in Tayside and Fife in 2015 and 2016

	2015(N=19,498)	2016(N=20,619)
Age (mean, SD)	59.01 (15.835)	58.31 (15.961)
Age group		
0-17	23 (0.1%)	29 (0.1%)
18-40	2,544 (13.0%)	2,937 (14.2%)
41-60	7,888 (40.5%)	8,402 (40.7%)
61-80	7,217 (37.0%)	7,452 (36.1%)
80+	1,826 (9.4%)	1,799 (8.7%)
Gender		
Female	12,107 (62.1%)	12,859 (62.4%)
Male	7,391 (37.9%)	7,760 (37.6%)
Health board		
Tayside	9,259 (47.5%)	9,407 (45.6%)
Fife	10,239 (52.5%)	11,212 (54.4%)
SIMD		
Missing	738 (3.8%)	820 (4.0%)
SIMD1	4,803 (24.6%)	5,093 (24.7%)
SIMD2	4,305 (22.1%)	4,575 (22.2%)
SIMD3	3,585 (18.4%)	3,817 (18.5%)
SIMD4	3,793 (19.5%)	3,968 (19.2%)
SIMD5	2,274 (11.7%)	2,346 (11.4%)
Rurality classification in Scotland		
Missing	738 (3.8%)	820 (4.0%)
Large urban	4,081 (20.9%)	4,106 (19.9%)
Other urban	9,137 (46.9%)	9,828 (47.7%)
Accessible small town	2,140 (11.0%)	2,265 (11.0%)
Remote small towns	288 (1.5%)	289 (1.4%)
Accessible rural	2,811 (14.4%)	3,003 (14.6%)
Remote rural	303 (1.6%)	308 (1.5%)
Average of prescription per person	5.83 (4.639)	5.94 (4.685)
Number of prescriptions	113,723	122,445
Range	1-36	1-33
Mean	5.83	5.94
Mode	1	1
Median	5	5
25% percentile	2	2
50% percentile	5	5
75% percentile	9	9

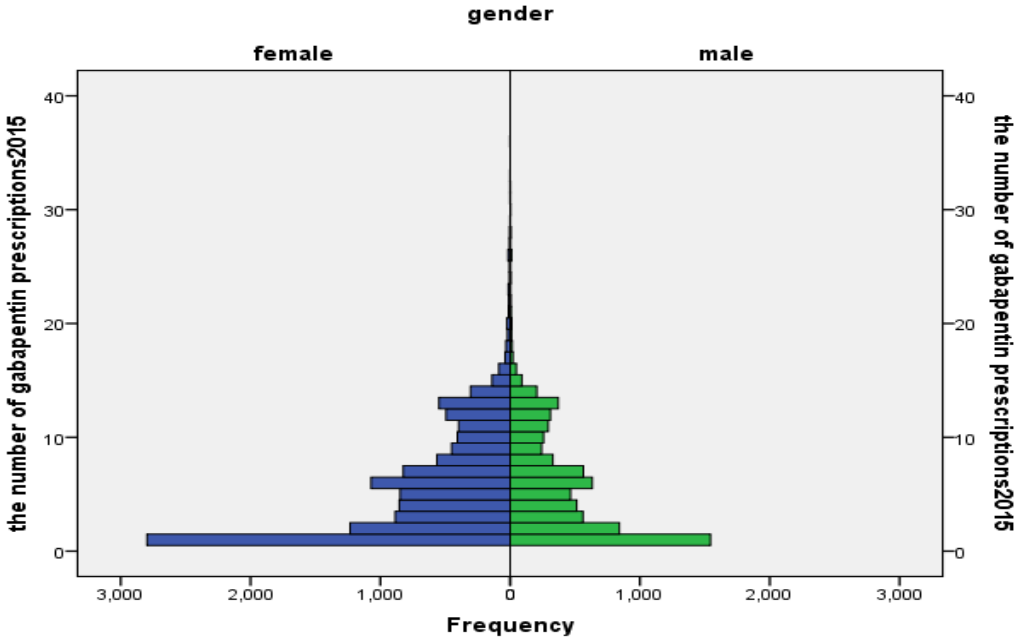

Figure 14. The distribution pattern of number of gabapentin prescriptions per patient per year, among those who received at least one prescription in Tayside and Fife in 2015

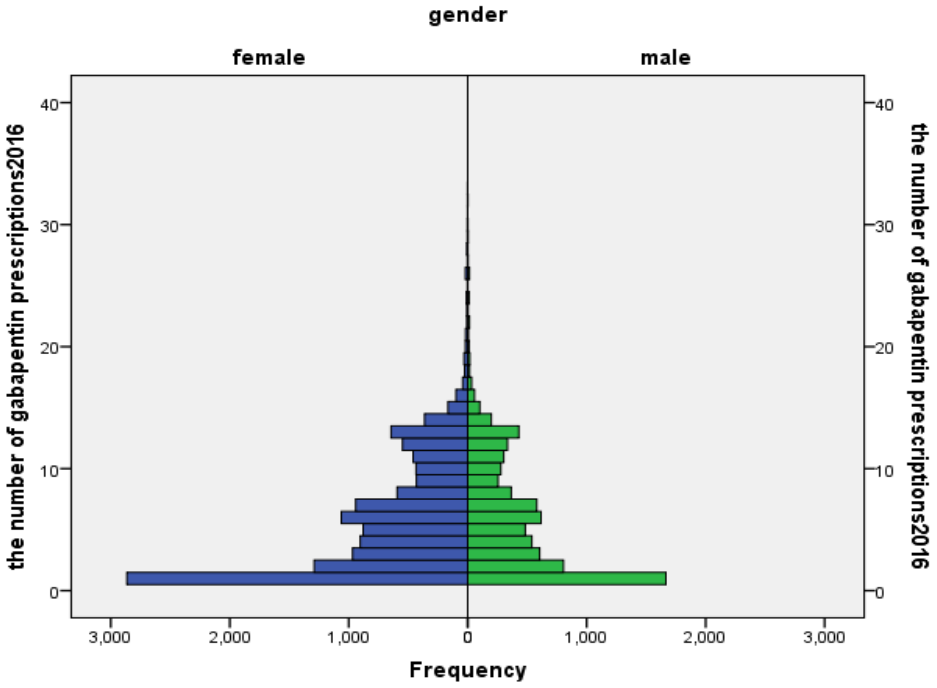

Figure 15. The distribution pattern of number of gabapentin prescriptions per patient per year, among those who received at least one prescription in Tayside and Fife in 2016

A total of 8,823 patients in 2015 and 10,280 patients in 2016 were prescribed pregabalin,

including patients who were prescribed both gabapentin and pregabalin in the same year. The mean age of patients was 57.71 and 56.68 in 2015 and 2016 respectively; most patients were in 41-60 years group (43.3% in 2015 and 43.9% in 2016); 5 patients and 751 patients were below 18 years old and over 80 years old in 2015 respectively, while for 2016 the numbers for these corresponding age groups were 7 patients and 829 patients (Table 7). Female patients accounted for 63.6% and 63.4% of prescriptions in 2015 and 2016 respectively; most patients were from Fife (65.7% in 2015 and 63.7% in 2016) (Table 7). The patients living in SIMD5 was the smallest proportion in 2015 (12.2%), and the same with 2016 (11.5%) (Table 7). The largest proportion of patients lived in Other urban area in 2015 and 2016 (37.6% and 38.8%), while the least proportion lived in remote rural area (1.9% in 2015 and 1.8% in 2016) (Table 7).

In 2015, the average number of pregabalin prescriptions per patient was 6.97, and the range was from 1 to 37; the median was 6 (Table 7). The number of pregabalin prescriptions per patient per year in 2015 was not normally distributed (Figure 16). Most patients received more than one prescription of pregabalin but the frequency of one prescription was the greatest in 2015 whether they were female or male patients (Figure 16), which was similar to the pattern of gabapentin prescriptions. The distribution pattern on the number of pregabalin prescriptions among male and female patients in 2016 was quite similar with that in 2015 (Table 7, Figure 17). The average number of pregabalin prescriptions was 7.16 and the range was 1~52 in 2016 (Table 7).

Table 7. The demographic characteristics of patients who received at least one pregabalin prescription in Tayside and Fife in 2015 and 2016

	2015 (N=8,823)	2016 (N=10,280)
Age (mean, SD)	57.71 (15.677)	56.68 (15.914)
Age group		
0-17	5 (0.1%)	7 (0.1%)
18-40	1,277 (14.5%)	1,700 (16.5%)
41-60	3,825 (43.3%)	4,511 (43.9%)
61-80	2,965 (33.6%)	3,233 (31.5%)
80+	751 (8.5%)	829 (8.1%)
Gender		
Female	5,610 (63.6%)	6,521 (63.4%)
Male	3,213 (36.4%)	3,759 (36.6%)
Health board		
Tayside	5,796 (65.7%)	6,546 (63.7%)
Fife	3,027 (34.3%)	3,734 (36.3%)
SIMD		
Missing	371 (4.2%)	462 (4.5%)
SIMD1	1,895 (21.5%)	2,270 (22.1%)
SIMD2	1,805 (20.5%)	2,166 (21.1%)
SIMD3	1,674 (19.0%)	1,938 (18.9%)
SIMD4	2,000 (12.7%)	2,262 (22.0%)
SIMD5	1,078 (12.2%)	1,182 (11.5%)
Rurality classification in Scotland		
Missing	371 (4.2%)	462 (4.5%)
Large urban	2,450 (27.8%)	2,743 (26.7%)
Other urban	3,314 (37.6%)	3,989 (38.8%)
Accessible small town	886 (10.0%)	1,059 (10.3%)
Remote small town	206 (2.3%)	233 (2.3%)
Accessible rural	1,426 (16.2%)	1,605 (15.6%)
Remote rural	170 (1.9%)	189 (1.8%)
Average of prescription per person	6.97 (5.1)	7.16 (5.284)
Number of prescriptions group	61,503	73,572
Range	1-37	1-52
Mean	6.97	7.16
Mode	1	1
Median	6	6
25% percentile	2	3
50% percentile	6	6
75 % percentile	11	11

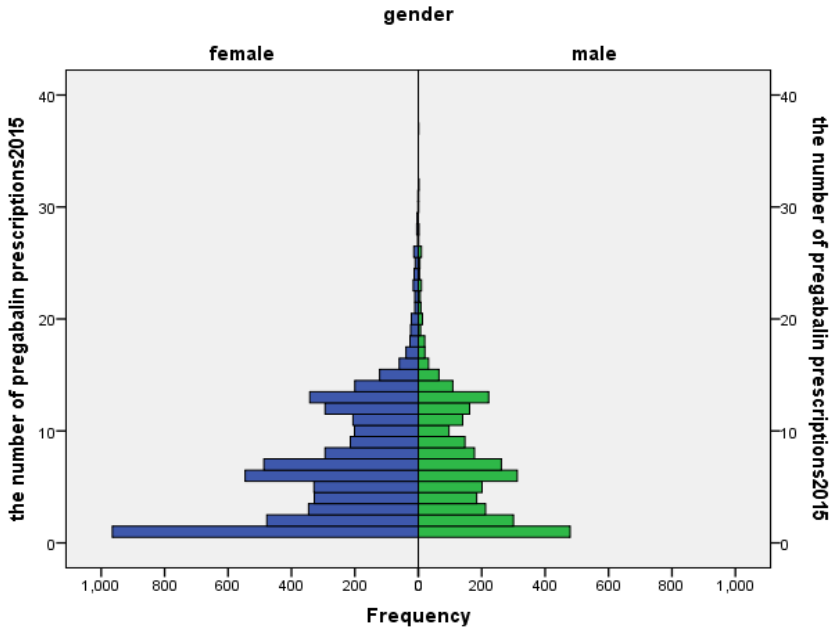

Figure 16. The distribution pattern of the number of pregabalin prescriptions each patient had per year in Tayside and Fife, among those who received at least one prescription in 2015

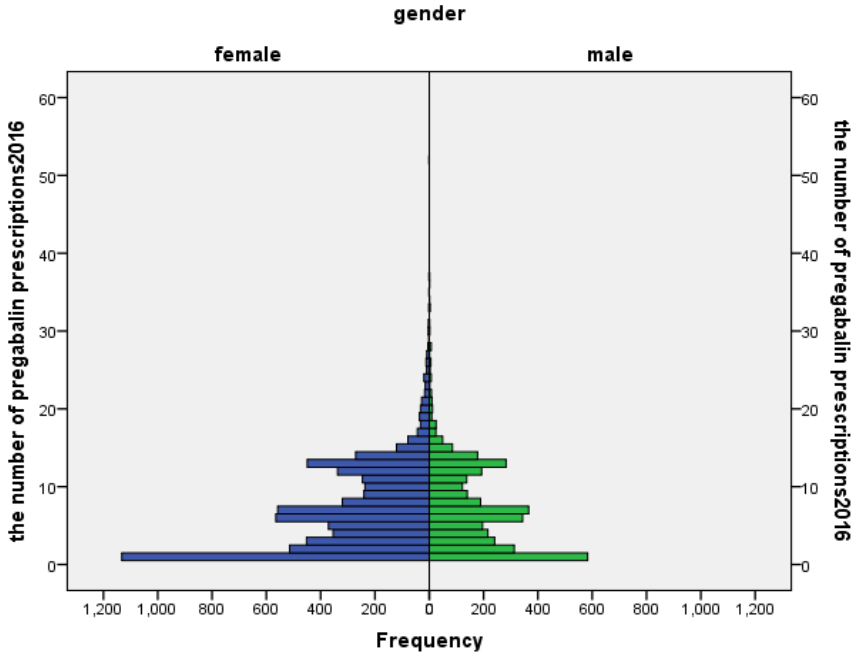

Figure 17. The distribution pattern of the number of pregabalin prescriptions each patient had per year in Tayside and Fife, among those who received at least one prescription in 2016

A total 1,684 patients were prescribed both gabapentin and pregabalin in Tayside and Fife in 2015 (Table 8). The average age for these patients was 56.61 (SD 15.66) (table

8). Overall, only two patients (0.1%) were under 18 years old and most patients (44.1%) were in the age group, 41-60 years old; 1,091 patients (64.8%) were female; and 978 patients (58.1%) were resident in Tayside (table 8). The range of the proportion of patients amongst the five SIMD categories was 11.3%~23.0% (table 8). There were 699 patients (41.5%) resident in other urban areas and 39 patients (2.3%) resident in remote small town. These patients received 6,413 prescriptions of gabapentin and 7,373 prescriptions of pregabalin totally in 2015, and average number of pregabalin prescriptions per patient received were more than that of gabapentin prescriptions (4.38 and 3.81prescriptions) (Table 8).

In 2016, there were 1,777 patients prescribed both gabapentin and pregabalin in Tayside and Fife (Table 8). The average age was 57.83 (SD 15.75) (Table 8). Overall, only two patients (0.1%) were under 18 years old and most patients (45.2%) were in the age group, 41-60 years old; 1,142 patients (64.3%) were female; and 924 patients (52.0%) were resident in Tayside (Table 8). The range of the proportion of patients amongst the five SIMD categories was 11.2%~25.4% (Table 8). There were 775 patients (43.6%) resident in other urban areas and 15 patients (0.8 %) resident in remote small town. These patients received 6,837 prescriptions of gabapentin and 7,559 prescriptions of pregabalin in total in 2016, and the average number of pregabalin prescriptions received per patient was more than that of gabapentin prescriptions (4.25 and 3.85 prescriptions) (Table 8).

Table 8. The demographic characteristics of patients who received both gabapentin and pregabalin in Tayside and Fife in 2015 and 2016

	2015 (N=1,684)		2016 (N=1,777)	
Age (mean, SD)		56.61(15.66)		57.83 (15.75)
Age group				
0-17		2 (0.1%)		2 (0.1%)
18-40		266 (15.8%)		341 (19.2%)
41-60		743 (44.1%)		803 (45.2%)
61-80		561 (33.3%)		528 (29.7%)
80+		112 (6.7%)		103 (5.8%)
Gender				
Female		1,091 (64.8%)		1,142 (64.3%)
Male		593 (35.2%)		635 (35.7%)
Health board				
Tayside		978 (58.1%)		924 (52.0%)
Fife		706 (41.9%)		853 (48.0%)
SIMD				
Missing		71 (4.2%)		81 (4.6%)
SIMD1		387 (23.0%)		452 (25.4%)
SIMD2		330 (19.6%)		394 (22.2%)
SIMD3		338 (20.1%)		314 (17.7%)
SIMD4		367 (21.8%)		337 (19.0%)
SIMD5		191 (11.3%)		199 (11.2%)
Rurality classification in Scotland				
Missing		71 (4.1%)		81 (4.6%)
Large urban		402 (23.9%)		431 (24.3%)
Other urban		699 (41.5%)		775 (43.6%)
Accessible small town		172 (10.2%)		201 (11.3%)
Remote small town		39 (2.3%)		15 (0.8%)
Accessible rural		261 (15.5%)		242 (13.6%)
Remote rural		40 (2.4%)		32 (1.8%)
Number of prescriptions group	gabapentin	Pregabalin	gabapentin	pregabalin
Sum	6,413	7,373	6,837	7,559
Range	1-29	1-25	1-31	1-28
Mean	3.81	4.38	3.85	4.25
Mode	1	1	1	1
Median	2	3	3	3

Overall, among the 36,800 patients who were prescribed a gabapentinoid, at least once in 2015 and 2016, 501 patients had at least one cancer episode. The mean age was 68.3; with 1.3% of female patients and 1.5% of male patients having cancer (Table 9). Patients of older age are more likely to have cancer (Table 9).

Table 9. The characteristics for patients with cancer episodes among patients who were prescribed a gabapentinoid at least once in Tayside and Fife in 2015 and 2016

	No cancer (n=36299)	At least one episode (n=501)
Age (mean, SD)	58.05 (16.1)	68.34 (14.6)
Age group		
0-17	45 (97.8%)	1 (2.2%)
18-40	5,445 (99.5%)	26 (0.5%)
41-60	14,799 (99.3%)	105 (0.7%)
61-80	12,781 (98.0%)	261 (2.0%)
80+	3,229 (96.8%)	108 (3.2%)
Gender		
Male	13,602 (98.5%)	202 (1.5%)
Female	22,697 (98.7%)	288 (1.3%)

Among the 36,800 patients, 2,357 patients died during 2015 and 2016 the average age was found to be 71. The proportion of dead patients in the age group 80+ was the largest (19.7%) (Table 10).

Table 10. The basic characteristics for patients who died among patients who were prescribed at least one gabapentinoid in Tayside and Fife in 2015 and 2016

	Dead (n=2,357)	Alive (n=34,443)
Age (mean, SD)	71.0 (14.7)	57.3 (15.9)
Age group		
0-17	2 (4.3%)	44 (95.7%)
18-40	79 (1.4%)	5,392 (98.6%)
41-60	447 (3.0%)	14,457 (97.0%)
61-80	1,172 (9.0%)	11,870 (91.0%)
80+	657 (19.7%)	2,680 (80.3%)
Gender		
Male	1,121 (8.1%)	12,689 (91.9%)
Female	1,236 (5.4%)	21,754 (94.6%)

The underlying cause of death was categorized into six groups. The most deaths were caused by neoplasms (1,068), which was reported as 45.3% (Table 11). Only 93 deaths were caused by disease of digestive system (Table 11).

Table 11. The underlying cause of death in patients prescribed gabapentinoids in 2015 and 2016 in Tayside and Fife.

Cause of death	*Frequency*	*Percent*
All circulatory system	**444**	**18.8%**
Acute myocardial infarction	98	22.1%
Ischaemic heart disease including angina	115	25.9%
Cerebrovascular disease	31	7.0%
Other circulatory system	200	45.0%
All neoplasms	**1,068**	**45.3%**
Neoplasms of the digestive organs	238	22.2%
Neoplasms of the respiratory and intrathoracic organs	304	28.4%
Other neoplasms	526	49.3%
Disease of respiratory system	**267**	**11.3%**
Pneumonia	63	23.6%
Chronic lower respiratory disease	133	49.8%
Other	71	26.6%
Disease of digestive system	**93**	**4.0%**
Disease of the nervous system	**103**	**4.4%**
All other causes	**382**	**16.2%**
Total	2,357	100%

Overall, among the total 36,800 patients, there were 10,629 (28.9%) patients using hospital admission services and 9,156 (24.9%) patients using A&E services. For hospital services, the average counts of attendance per patient was 2.96 (±3.4) and the range was 1 to 66 (Table 12-a). The mean of average length each patient stayed was 3.2 days and the length of stay ranged from 0 to 290 days (Table 12-b). For A&E services the mean of counts of attendance per patient was 1.69 (±2.0) and the range was 1 to 83 (Table 12-a).

Table 12-a. The descriptive analysis for hospital admission and A&E admission

	Number of patients	Minimum of counts	Maximum of counts	Sum of counts	Average counts per patient	SD
counts of admission	10,629	1	66	31,507	2.96	3.4
counts of A&E	9,156	1	83	15,484	1.69	2.0

Table 12-b. The descriptive analysis for length of stay at hospital admission with 10,629 patients

	Minimum	Maximum	Mean	SD
average length of stay per patient	0.0	201.0	3.2	6.6
min of length per patient	0	201	1.3	4.3
max of length per patient	0	290	7.0	15.9

3.3.3. Logistic regression model

The association between demographic factors and prescription of pregabalin rather than gabapentin in 2015 and 2016 was examined by logistic regression modelling.

In 2015, there were 24,953 patients prescribed only gabapentin or only pregabalin, only 23,986 patients with complete information; 967 patients missing information on SIMD and rurality factors. Thus, the population the logistic regression model analysed was 23,986 patients who were prescribed only gabapentin or only pregabalin, excluding patients who were prescribed both gabapentin and pregabalin. The positive outcome was pregabalin prescribed and the negative one was gabapentin prescribed. Patients resident in Fife were more likely to be prescribed gabapentin other than pregabalin than patients in Tayside (P <0.001) (Table 13). Patients resident in the most deprived areas were more likely to be prescribed gabapentin rather than pregabalin than patients resident in more affluent areas (P<0.001) (Table 13). Patients resident in accessible small towns and accessible rural area were more likely to prescribed pregabalin rather than gabapentin, compared with patients living in other urban area (both P = 0.01) (Table 13). Patients aged 61-80 and 80+ were more likely to be prescribed gabapentin rather than pregabalin than patients aged 41-60 (P <0.001) (Table 13).

Table 13. The association between demographic factors and prescription of pregabalin rather than gabapentin in 2015 among patients who only received gabapentin or pregabalin.

	Estimated effect size	*S.E.*	*P-value*	*OR*	*95% C.I.for OR* *Lower*	*Upper*
Age						
0-17	-0.98	0.63	0.12	0.38	0.11	1.29
18-40	0.03	0.05	0.49	1.03	0.94	1.13
61-80	-0.19	0.03	<0.01	0.86	0.77	0.88
80+	-0.24	0.05	<0.01	0.79	0.71	0.86
41-60			Reference category			
Gender						
Male	-0.06	0.03	0.06	0.94	0.89	1.00
Female			Reference category			
Health board						
Fife	-0.84	0.04	<0.01	0.43	0.40	0.47
Tayside			Reference category			
SIMD						
SIMD2	0.18	0.05	<0.01	1.19	1.09	1.30
SIMD3	0.25	0.05	<0.01	1.29	1.17	1.42
SIMD4	0.26	0.05	<0.01	1.29	1.18	1.42
SIMD5	0.26	0.05	<0.01	1.30	1.17	1.44
SIMD1			Reference category			
Rurality						
Large urban	0.07	0.04	0.09	1.08	0.99	1.17
Accessible small towns	0.14	0.05	0.01	1.15	1.04	1.27
Remote small towns	0.19	0.11	0.07	1.21	0.98	1.49
Accessible rural area	0.13	0.05	0.01	1.13	1.04	1.25
Remote rural area	-0.14	0.11	0.23	0.87	0.70	1.09
Other urban			Reference category			

In 2016, there were 27,345 patients prescribed only gabapentin or only pregabalin, only 26,225 patients with complete information; 1,120 patients missing information on SIMD and rurality factors. Thus, the population the logistic regression model analysed was 26,225 patients were prescribed only gabapentin or only pregabalin, excluding patients who were prescribed both gabapentin and pregabalin. The positive outcome was pregabalin prescribed. Patients resident in Fife were more likely to prescribe gabapentin other than pregabalin than patients in Tayside (P <0.001) (Table 14). Patients resident in the most deprived areas were more likely to be prescribed gabapentin rather than pregabalin than patients in other socioeconomic classes (P<0.001) (Table 14). Patients resident in accessible small towns and accessible rural area were more likely to be prescribed pregabalin rather than gabapentin than patients in other urban area (P<0.001 and =0.01 respectively) (Table 14). Compared with patients aged 41-60, patients aged 18-40 were 41.2% more likely to be prescribed pregabalin rather than gabapentin (P<0.001), while patients aged 61-80 were 6% less likely to be prescribed pregabalin (P=0.04) (Table 14).

Table 14. The association between demographic factors and prescription of pregabalin rather than gabapentin in 2016 among patients who only received gabapentin or pregabalin.

	Estimated effect size	S.E.	P-value	OR	95% CI for OR	
					Lower	Upper
Age						
0-17	0.59	0.45	0.19	1.80	0.75	4.34
18-40	0.35	0.04	<0.01	1.41	1.30	1.53
61-80	-0.06	0.03	0.04	0.94	0.89	1.00
80+	-0.02	0.05	0.66	0.98	0.89	1.08
41-60	Reference category					
Gender						
Male	0.02	0.03	0.48	1.02	0.97	1.08
Female	Reference category					
Health board						
Fife	-0.45	0.03	<0.01	0.64	0.60	0.68
Tayside	Reference category					
SIMD						
SIMD2	0.20	0.04	<0.01	1.23	1.14	1.32
SIMD3	0.33	0.04	<0.01	1.40	1.28	1.52
SIMD4	0.37	0.04	<0.01	1.44	1.32	1.57
SIMD5	0.52	0.05	<0.01	1.68	1.54	1.85
SIMD1	Reference category					
Rurality						
Large urban	0.05	0.04	0.21	1.05	0.97	1.14
Accessible small towns	0.15	0.04	<0.01	1.17	1.07	1.27
Remote small towns	0.19	0.11	0.08	1.20	0.98	1.48
Accessible rural area	0.11	0.04	0.01	1.12	1.03	1.22
Remote rural area	0.12	0.11	0.26	1.13	0.91	1.40
Other urban	Reference category					

3.3.4. Poisson regression model

The associations between the demographic factors and the number of gabapentinoids prescribed in 2015 and 2016 were evaluated by using the Poisson regression model (Tables 15-18). Gabapentin and pregabalin were examined separately.

The study population for the first Poisson model was those patients who were prescribed gabapentin at least once in 2015. The results showed that male patients were more likely to receive a larger number of gabapentin prescriptions than female

patients were (P<0.001). Patients living in Tayside and the most deprived areas (SIMD1) were more likely to receive more gabapentin prescriptions compared with patients in Fife and more affluent areas (both P-value<0.001). As age increased, patients were more likely to receive more gabapentin prescriptions in 2015 (P-value<0.001). Compared with other urban areas, patients in large urban areas were likely to receive fewer less gabapentin prescriptions (P=0.01). There was no significant association between other rurality groups and the other urban group (Table 15).

Table 15. The first Poisson model- association between demographic factors and the number of gabapentin prescriptions in 2015 among patients who were prescribed gabapentin at least once

Variables	*Estimated effect size*	*SE*	*95% Wald Confidence Interval*		
			Lower	*Upper*	*p-value*
(Intercept)	1.87	0.02	1.84	1.90	<0.01
Gender					
Male	0.02	0.01	0.01	0.04	<0.01
Female			Reference category		
Health board					
Fife	-0.09	0.01	-0.11	-0.07	<0.01
Tayside			Reference category		
SIMD					
SIMD2	-0.09	0.01	-0.11	-0.07	<0.01
SIMD3	-0.15	0.01	-0.17	-0.13	<0.01
SIMD4	-0.21	0.01	-0.23	-0.19	<0.01
SIMD5	-0.29	0.01	-0.31	-0.27	<0.01
SIMD1			Reference category		
Rurality					
Large urban	-0.03	0.01	-0.05	-0.01	0.01
Accessible small towns	-0.01	0.01	-0.03	0.01	0.54
Remote small towns	0.01	0.03	-0.04	0.06	0.57
Accessible rural area	0.01	0.01	-0.01	0.03	0.43
Remote rural area	-0.03	0.03	-0.08	0.02	0.23
Other urban			Reference category		
Age	0.01	0.01	0.01	0.01	<0.01

The study population for the second Poisson model was the patients who received at least one gabapentin prescription in 2016. Older age was related to more gabapentin prescriptions (P<0.001). Patients resident in Tayside and the most deprived areas (SIMD1) were more likely to be prescribed more gabapentin prescriptions in 2016 compared with patients in Fife and more affluent areas (both P<0.001), while patients living in large urban and accessible rural area were more likely to receive fewer gabapentin prescriptions than those in other urban areas in 2016 (P<0.001). However, after controlling other demographic variables, gender was not significantly related to the number of gabapentin prescriptions received (Table 16).

Table 16. The second Poisson model- association between the demographic factors and the number of gabapentin prescribed in 2016 among patients who prescribed gabapentin at least once in 2016

Variables	*Estimated effect size*	*SE*	*95% Wald Confidence Interval*		*P-value*
			Lower	*Upper*	
(Intercept)	1.89	0.01	1.86	1.92	<0.01
Gender					
Male	0.01	0.01	-0.01	0.02	0.07
Female			Reference category		
Health board					
Fife	-0.09	0.01	-0.11	-0.07	<0.01
Tayside			Reference category		
SIMD					
SIMD2	-0.07	0.01	-0.08	-0.05	<0.01
SIMD3	-0.15	0.01	-0.17	-0.13	<0.01
SIMD4	-0.22	0.01	-0.24	-0.20	<0.01
SIMD5	-0.29	0.01	-0.30	-0.26	<0.01
SIMD1			Reference category		
Rurality					
Large urban	-0.06	0.01	-0.07	-0.03	<0.01
Accessible small towns	-0.01	0.01	-0.03	0.01	0.16
Remote small towns	-0.01	0.02	-0.06	0.03	0.55
Accessible rural area	-0.03	0.01	-0.04	-0.01	0.01
Remote rural area	-0.03	0.02	-0.07	0.02	0.30
Other urban			Reference category		
Age	0.01	0.01	0.01	0.01	<0.01

The study population for the third Poisson model was the patients who had at least one pregabalin prescription in 2016. Older patients received less number of pregabalin prescriptions being issued (P<0.001). Tayside and SIMD1 residence were factors associated with a higher number of pregabalin prescriptions (both P<0.001), while there was no significant difference between those in the SIMD2 quintile and SIMD1 quintile. Additionally, there were no significant associations between gender, rurality and the number of pregabalin prescriptions (Table 17).

Table 17. The third Poisson model- association between the demographic factors and the number of pregabalin prescribed in 2015 among patients who prescribed pregabalin at least once in 2015

Variables	*Estimated effect size*	*SE*	*95% Wald Confidence Interval*		*P-value*
			Lower	*Upper*	
(Intercept)	2.14	0.02	2.10	2.18	<0.01
Gender					
Male	0.01	0.01	-0.01	0.03	0.06
Female			Reference category		
Health board					
Fife	-0.10	0.01	-0.12	-0.08	<0.01
Tayside			Reference category		
SIMD					
SIMD2	0.01	0.01	-0.02	0.02	0.75
SIMD3	-0.07	0.01	-0.09	-0.04	<0.01
SIMD4	-0.09	0.01	-0.12	-0.06	<0.01
SIMD5	-0.16	0.01	-0.19	-0.13	<0.01
SIMD1			Reference category		
Rurality					
Large urban	-0.01	0.01	-0.03	0.01	0.25
Accessible small towns	-0.02	0.01	-0.05	0.01	0.09
Remote small towns	0.04	0.02	-0.01	0.09	0.09
Accessible rural area	0.01	0.01	-0.02	0.02	0.93
Remote rural area	0.03	0.03	-0.02	0.09	0.22
Other urban			Reference category		
Age	-0.01	<0.01	-0.01	-0.01	<0.001

The study population of the fourth Poisson model was patients who had at least one pregabalin prescription in 2016. Being resident in Tayside or in the most deprived areas would increase the likelihood of receiving more pregabalin prescriptions (both P<0.001), while there was no significant difference between SIMD2 and SIMD1 quintiles. Older age would decrease the likelihood of receiving more pregabalin prescriptions (P<0.001). Compared with patients living in other urban areas, patients living in remote small towns were more likely to receive more pregabalin prescriptions (P=0.01). Gender was not significantly related to the number of pregabalin prescriptions (Table 18).

Table 18. The fourth Poisson model- association between the demographic factors and the number of pregabalin prescribed in 2016 among patients who prescribed pregabalin at least once in 2016

Variables	*Estimated effect size*	*SE*	*95% Wald Confidence Interval*		*P-value*
			Lower	*Upper*	
(Intercept)	2.17	0.01	2.14	2.21	<0.01
Gender					
Male	0.01	0.01	-0.01	0.03	0.14
Female			Reference category		
Health board					
Fife	-0.10	0.01	-0.12	-0.09	<0.01
Tayside			Reference category		
SIMD					
SIMD2	-0.01	0.01	-0.04	0.01	0.13
SIMD3	-0.08	0.01	-0.11	-0.06	<0.01
SIMD4	-0.11	0.01	-0.14	-0.09	<0.01
SIMD5	-0.19	0.01	-0.22	-0.16	<0.01
SIMD1			Reference category		
Rurality					
Large urban	-0.02	0.011	-0.04	<0.01	0.05
Accessible small towns	-0.01	0.013	-0.03	0.01	0.61
Remote small towns	0.08	0.024	0.03	0.13	0.01
Accessible rural area	-0.01	0.012	-0.04	0.01	0.15
Remote rural area	0.04	0.028	-0.01	0.10	0.11
Other urban			Reference category		
Age	>-0.01	<0.01	>-0.01	>-0.01	<0.01

3.3.5. Age standardised mortality

The age standardised mortality risk for overall deaths in the population prescribed gabapentinoids was 3.93 (CI 3.82-4.05) times higher than that in the Scottish general population during 2015 & 2016 combined (Table 19). The age standardised death rate risks for circulatory deaths and respiratory deaths in our study population were 2.10 and 2.56 times that of the Scottish population (Table 19). All the findings were statistically significant (P<0.001) (Table 19).

Table 19. The comparison of age standardised mortality (per 100,000 persons) between Scotland and those prescribed a gabapentinoid at least once in Tayside and Fife in 2015 and 2016

Cause of death	*Age standardised death rate -gabapentinoids population*	*Age standardised death rate -Scotland population*	*Relative risk (95% CI)*	*P-value*
Overall	4,550.85	1,156.85	3.93 (3.82-4.05)	<0.001
Circulatory	664.15	315.8	2.1 (1.95-2.27)	<0.001
Respiratory	394.06	154.15	2.56 (2.32-2.81)	<0.001

3.4. Discussion

This study is the first study to quantify the trends of gabapentin or pregabalin prescribing in Tayside, Fife and Scotland. This study used the number of gabapentin or pregabalin prescriptions and the number of patients who were prescribed at least one gabapentin or pregabalin. The prevalence of prescriptions and number of patients were also calculated to quantify and compare the gabapentin or pregabalin prescribing rates between Tayside, Fife and Scotland. It was found that the number of gabapentin prescriptions increased in Fife from 2010 to 2016 (around a 3-fold increase from 2010 to 2016); in Tayside, the number of gabapentin prescriptions increased from 2006 to 2010 and then slightly decreased in 2010/11 and then increased gradually from 2011 to 2016 (around 3.5-fold increase in 2016 compared with 2006). The number of patients who were prescribed gabapentin at least once increased in Tayside from 2006 to 2016 (a 4-fold increase) and Fife from 2010 to 2016 (a 2.65-fold increase). In Fife, the prevalence of gabapentin prescribing increased rapidly from 2010 to 2016; in Tayside and Scotland, there were a slight decrease in 2011 before rising. The prevalence of gabapentin prescribing in Scotland was a little higher than in Tayside every year from 2006 to 2016, while the prevalence in Fife exceeded that in Scotland in 2013. The number of patients who were prescribed gabapentin at least once increased in Tayside and Fife and it was higher in Fife than in Tayside after 2012. The number of pregabalin prescriptions increased dramatically in Tayside (a 21.5-fold increase) and

Scotland (a 16-fold increase) from 2006 to 2016 and it increased gradually in Fife from 2010 to 2016 (around a two-fold increase). The number of patients who were prescribed pregabalin at least once increased in Tayside from 2006 to 2016 (a 15-fold increase), while it slightly decreased in Fife in 2012 before rising. The prevalence of pregabalin prescribing was higher in Tayside than in Fife and Scotland from 2011. The number of patients who were prescribed pregabalin at least once was higher in Tayside than in Fife from 2011. From the NHS Digital prescribing cost analysis website, it was found that in England, the number of gabapentin prescription items increased from 2010 to 2015, with 2,435,500 prescriptions (2010), 2,905,800 prescriptions (2011), 3,531,900 prescriptions (2012), 4,212,300 prescriptions (2013), 4,978,900 prescriptions in (2014), and 5,723,000 prescriptions in (2015) (59–64). The number of pregabalin prescriptions increased by 182% in England from 2010 to 2015, with 1,698,300 prescriptions (2010), 2,205,400 prescriptions (2011), 2,730,700 prescriptions (2012), 3,349,800 prescriptions (2013), 4,086,400 prescriptions (2014), and 4,801,600 prescriptions (2015) (59–64). The numbers of gabapentin prescriptions and pregabalin prescriptions were much higher in England than that in Scotland every year from 2010 to 2015. That is mainly because the population is 10 times higher in England than that in Scotland (65).

The prescribing dataset in this study is from GP prescribing records and is provided by HIC. It is a community-dispensed prescription dataset, so most prescriptions were written by GPs and only a small number of prescriptions were written by nurses, pharmacists and dentists. The dataset also includes prescriptions written in hospital but dispensed in the community but excludes the prescriptions within hospitals. It also excludes the prescriptions in prison and private prescriptions. Thus, the number of gabapentin and pregabalin prescriptions in Tayside and Fife may be a little underestimated, but it was comparable with Scottish national data which was summarised by ISD from community-dispensed dataset, and the number excluded from the dataset is likely to be a very small proportion of the total (66).

The main reasons for choosing data from Tayside and Fife were practical. The way for us to access the data was through HIC from which complete, high quality prescribing data relating to each patient in Tayside and Fife was available. Using the CHI number, we could also utilise HIC collected data in relation to cancer, death and use of hospital services. This level of individual data and linkage would not have been practical further afield, including elsewhere in Scotland. Thus, Tayside and Fife were the ideal setting to identify the possible factors related to gabapentinoids prescribing and its outcomes, in order to improve the safety of gabapentinoids usage.

Our study began in 2017, so we chose the latest available full year of data which was in 2016. This epidemiology study aimed to calculate the gabapentinoids use over 10 years, to illustrate the changes in rates in these two health boards. However, prescribing data from Fife only became available to HIC from 2010 and so only Tayside could provide data for the full 10-year period. For the investigation of health outcomes and use of health service, this study only used data in 2015 and 2016, because cancer, death, hospital admission, A&E and outpatient admission datasets provided by HIC were only provided for 2015 or 2016.

In Scotland, gabapentin and pregabalin are both licensed as treatment for peripheral neuropathic pain and focal seizures, while pregabalin is also licensed for central neuropathic pain and general anxiety disorder (GAD) (25,67). Thus, the overall trends of gabapentinoids prescribing may suggest there was a rise in the prevalence of neuropathic pain and epilepsy with focal seizures in Tayside, Fife and Scotland. However, other studies also found gabapentinoids prescribing for unlicensed indications and these indications were for other types of pain, including migraine, sciatica, arthritis; methadone reduction; chest pain (30). Thus, if the growth of gabapentin and pregabalin prescriptions could not be totally explained by an increasing prevalence of neuropathic pain, epilepsy and GAD, it could also be due to a switch to these drugs from other drugs previously used to treat neuropathic pain or a greater awareness of the need to treat neuropathic pain following newly published evidence(68).

This would be consistent with recent evidence which showed there was a rise in gabapentinoids misuse and abuse (25,69,70). To identify the reason why there was a rapid increase in gabapentinoids prescribing, a further study on the trends of patients with neuropathic pain, epilepsy and GAD should be investigated and the size of gabapentinoids misuse in Tayside and Fife also should be identified.

For the data-linkage, there were 36,800 patients prescribed a gabapentinoid at least once in Tayside and Fife in 2015 and 2016. The distributions of number of gabapentin or pregabalin prescriptions for each patient each year were positively skewed, and they were all similar in male and female. The frequency of one prescription of gabapentin or pregabalin receiving in one year was the greatest whether they were female or male patients in 2015 and 2016 (figure 14), but more patients received more than one prescription and the ranges in the number of gabapentin and pregabalin prescriptions were 1 to 36 and 1 to 52 in 2015 and 2016. The ranges might simply represent more prescriptions with fewer tablets each time in a positive aspect, which means patients are at less risk of overdose, while negatively, drug overdose and repeat prescription availability may also need to be recognised. These findings suggest that a further study on whether overdose and repeat prescriptions were received by patients every year is needed. Even though there is a proposal to reclassify gabapentin and pregabalin as C Controlled Drugs which means a repeat prescription would not be established (71), the process still needs more evidence. Thus, the large number of prescriptions per patient per year in Tayside and Fife and the rapid increase of gabapentinoids prescriptions suggest that further study on repeat prescriptions available could provide some evidence for the proposal above. It was also found there were patients prescribed both gabapentin and pregabalin in 2015 and 2016, which means some patients switched between gabapentin and pregabalin (72). Therefore, it also could be hypothesized that part of the changes in gabapentinoids prescribing rates may be due to the switch between gabapentin and pregabalin.

According to the search of systematic reviews, there were no studies investigating the association between the gabapentin or pregabalin prescribing and demographic factors, so this study is the first study to identify the potential factors which may influence the gabapentin or pregabalin prescribing, using two different statistics model to investigate the associations, logistic regression model and Poisson regression model.

Poisson modelling was used to identify whether there was association between demographic factors and the number of gabapentin or pregabalin prescriptions received. It was found there was a significant association between Health Board, deprivation, age and rurality and the number of gabapentin prescriptions received. Patients resident in Tayside and SIMD1 were more likely to receive a larger number of gabapentin and pregabalin prescriptions per year in 2015 and 2016. Similar associations were found in a study of the epidemiology of opioids prescribing in Scotland (73). As the age increased, the average number of gabapentin prescriptions per patient was larger, while the number of pregabalin prescriptions per patient was smaller. These findings were consistent with the results from the logistic regression model in this study. Patients in younger age groups were more likely to be prescribed pregabalin rather than gabapentin. Patients resident in Fife and SIMD1 were more likely to be prescribed gabapentin rather than pregabalin. The reasons for these differences are probably partly due to the different prevalence of neuropathic pain, epilepsy and GAD in different age groups and different socioeconomic classes. Because gabapentin and pregabalin are both licensed for focal seizures and peripheral neuropathic pain (67), another reason may lie in the choice of gabapentin or pregabalin by GPs or the requests of patients. Gabapentin is recommended as the 1st or 2nd line for neuropathic pain and pregabalin should only be used if gabapentin is not tolerated or ineffective (11). There is a report about the concerns on the choice of gabapentin and pregabalin in UK (74). This report (74) illustrated that gabapentin and pregabalin both have a high efficacy in treatment of peripheral neuropathic pain with a number needed to treat (NNT) of 4.2 for pregabalin and NNT of 5.1 for gabapentin to achieve a 50% pain relief and with similar side-effects, while pregabalin is more cost effective with simple dosing and titration. However,

gabapentin is much cheaper than pregabalin and the price comes from the prescribing budget, so there is a choice for NHS that with the same level of investment, is it better to treat more patients with the cheaper one but seemingly less effective or to treat fewer patients with the more expensive one but seemingly more effective and simple (74). These findings may raise a hypothesis that age, and socioeconomic circumstances will influence the number of gabapentin or pregabalin prescriptions and the choice of gabapentin and pregabalin for the same disease.

The age standardised mortality among the population prescribing gabapentinoids was 3.93 times higher than that among the Scottish general population, which suggested gabapentinoids prescribing might be associated with higher mortality. This finding is consistent with recent published evidence (25,75,76). However, it does not take account of the reasons for prescribing, and adverse selection which means that those who are prescribed a gabapentin are more likely to be sicker than the average person in the population. This preliminary finding needs further investigation, including comparison between similar populations (those with treatment for other chronic conditions) and those with neuropathic pain who are not prescribed gabapentinoids.

This study illustrated the prescribing trends of gabapentin and pregabalin and the distribution of gabapentinoids prescribing among demographic factors. There are some strengths in this study. Firstly, the datasets were cleaned and managed well before they underwent the further analysis. The GP gabapentinoids prescribing datasets in 2015 and 2016 were merged into one dataset (Dataset 2) with the form, single record for each patient, including the number of gabapentin or pregabalin prescriptions in 2015 and 2016 respectively and there were 36,800 patients included. The duplications and 214 cases missing Pro-CHI were removed. The demographic file, A&E dataset, hospital admission file, cancer registration file, death file and outpatient admission file were linked with Dataset 2 by matching the Pro-CHI of patients, the unique identifier. This linking is only possible in Scotland where each individual has a unique CHI number, shared across all health-related datasets. Dataset

2 determined the number of patients and the other datasets were only used to add the variables not influencing the final size. The data linkage added more variables into the dataset and made the dataset more comprehensive for data analysis. Secondly, the age standardised mortality among the population prescribed gabapentinoids was compared with the Scottish general population, which implied an association between gabapentinoids prescribing and death. Thirdly, this study summarised the pattern of health service use among population with gabapentinoids prescribing, which contributed to a further analysis of the associations between gabapentinoids prescribing and health service use after adjusting for confounders. Additionally, this study summarised the main causes of death among patients with gabapentinoids prescribing, which could be used to generate hypotheses about the associations between underlying death cause and gabapentinoids prescribing to understand the potential health problem caused by gabapentinoids. Another strength of this study is that it used two kinds of statistics model, logistic regression model and Poisson model, to identify the associations between gabapentinoids prescribing and demographic factors. The two kinds of model have different functions and were mutually complementary in this study. The logistic regression model was to identify how the factors influenced the likelihood of being prescribed pregabalin rather than gabapentin and the Poisson model was to identify which factors increased the likelihood of receiving a higher number of gabapentin or pregabalin prescriptions. These findings could help us propose specific hypotheses about the risk factors and reasons related gabapentinoids prescribing.

However, this study still has some limitations. First, the most important limitation is that this study failed to compare health outcomes (hospital attendance, outpatient attendance, A&E attendance, cancer, mortality) or demographic factors between people who had received a gabapentinoid and those who had not, which would have been the ideal analysis to test the associations. However, due to the dataset we had, we did not have the data on people who had not received a gabapentinoid. Thus, this study could only compare these factors between those who had received gabapentin and those had received pregabalin. Second, due to the limitation of the data platform, 214 cases

missing Pro-CHI were removed before dataset linkage, because these non-completed cases could not be matched with other variables without this unique identifier. Thus, the information from these 214 patients was not analysed and this might bias the distribution among demographic factors. However, this was a very small proportion of the total number who received a gabapentinoid prescription. Thirdly, the demographic file provided by HIC included 22 variables, but some of them conveyed the same information, such as SIMD with five classifications and SIMD with ten classifications, date of birth and age, rurality with different classifications. The demographic factors chosen in this study only included age, gender, SIMD with five classifications, rurality with six classifications and Health Board. Even though this study examined the associations with the five demographic factors and gabapentinoids prescribing, there are still many other potential confounders not adjusted for, such as education background, type of work, type of family, marriage status, alcohol, smoking status and disease history which are related to neuropathic pain, epilepsy and GAD (77–79). Then, this study failed to examine the association of gabapentinoids prescribing with health service use and cancer, because there were many other factors related to health service use and cancer episodes, and these potential confounders, such as disease history, diagnosed main health problem, were not provided by the original datasets. The original dataset did not provide the reasons for gabapentin or pregabalin prescriptions, so we could not find the pattern of reasons why gabapentin and pregabalin were prescribed. Thus, we could not find the reasons to explain the trends and associations with demographic factors, but only generated hypotheses. Finally, the original prescribing datasets provided all gabapentin and pregabalin prescriptions from 2006 to 2016. However, this study did not analyse all patients prescribed pregabalin from 2006, but only prescribing data in 2015 and 2016 to identify the associations. The associations may vary in different years.

This study is an epidemiological study to quantify the trends of gabapentin and pregabalin prescribing and describe the distribution pattern of prescriptions among demographic categories, which can help us to understand the breadth of gabapentin and

pregabalin prescribing and generate hypotheses about the reasons. Additionally, this study will contribute to a planned programme studying gabapentinoids prescribing in Scotland, to investigate the reasons, to quantify the indications of gabapentin and pregabalin prescribed, to find the details about gabapentinoids misuse and abuse in Scotland and determine associated health problems. This is likely to inform policy and practice relating to gabapentinoids prescribing in Scotland and further afield.

3.5. Conclusion

The overall trends of gabapentin and pregabalin prescribing in Tayside and Scotland from 2006 to 2016 and Fife from 2010 to 2016 are rising. It was found that age, deprivation, Health Board area of residence and some levels of rurality were associated with gabapentin and pregabalin prescribing, and also associated with the number of gabapentin and pregabalin prescriptions received. The age standardised mortality among those receiving at least one gabapentinoid prescription was higher than in the Scottish general population. Further study on the reasons, indications, determinants, and associations of gabapentinoids prescribing with health problems is needed.

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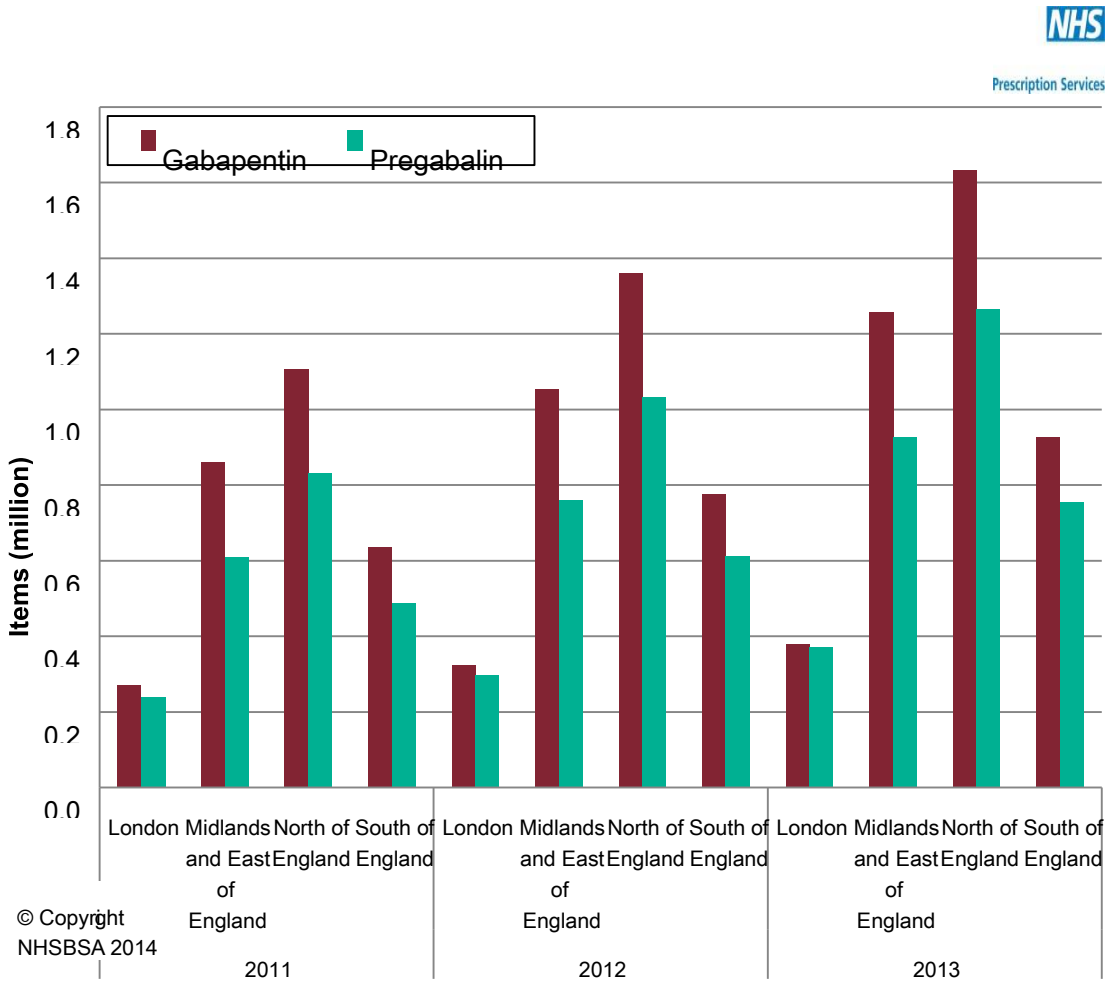
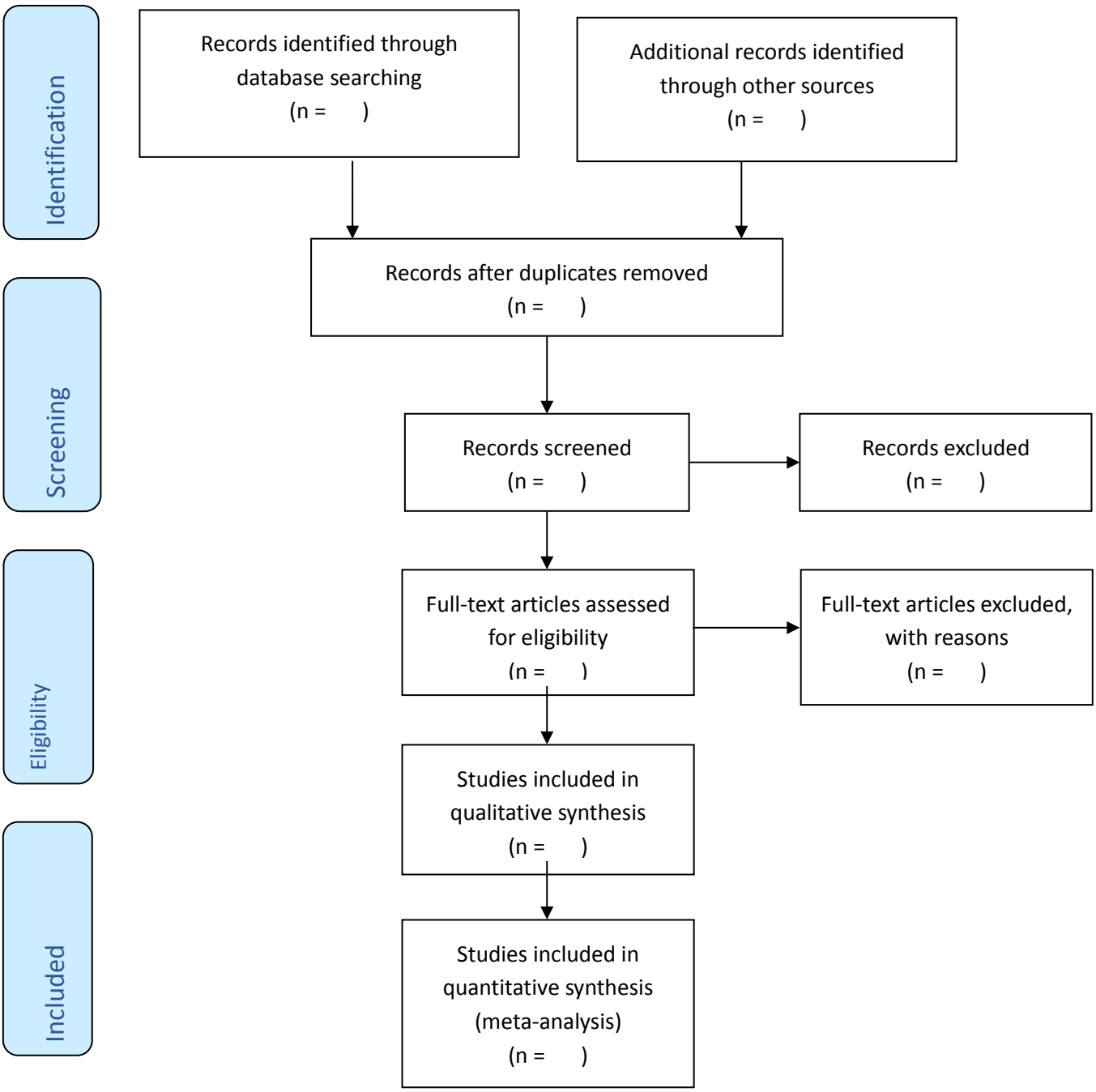
5. Appendix

Appendix 1. The statistics of gabapentinoids prescribing varying across NHS England regions



Picture source: Public Health England, NHS, the Advice for prescribers on the risk of the misuse of pregabalin and gabapentin (25)

Appendix 2. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart



Appendix 3. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist

Section and Item	Item No.	Recommendation	Reported on Page No.
Title and Abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/Rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study Design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	

Section and Item	Item No.	Recommendation	Reported on Page No.
Data Sources/ Measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study Size	10	Explain how the study size was arrived at	
Quantitative Variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical Methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	

Section and Item	Item No.	Recommendation	Reported on Page No.
Descriptive Data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome Data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main Results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other Analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key Results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	

Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other Information			
Section and Item	**Item No.**	**Recommendation**	**Reported on Page No.**
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

***Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Appendix 4. The data abstraction form of this systematic review

data abstraction form					
title					
author		published year		country	
research question related to gabapentin or pregabalin					
methods					
study design					
setting location					
study period	recruitment date				
	exposure date				
	follow-up				
	data period				
data source					
study population	target population				
	clinical status				
	cases	exposure			
	cohorts	number of groups			
		exposure			
gabapentin		pregabalin		both	
results					
study population	sample size		missing number		
	age range		adults selected out or not		
definition of outcome interested					
prescribing rate					
prescribing trend					
main findings	prescribing trend				
	related demographic factors				

	related health outcomes	
limitations		
sample size too small		
only prescribing portion		
no age information		
data source		
others		

Appendix 5. The National Heart, Lung and Blood Institute (NHLBI)

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			

Criteria	Yes	No	Other (CD, NR, NA)*
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Quality Rating (Good, Fair, or Poor)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

*CD, cannot determine; NA, not applicable; NR, not reported

Guidance for Assessing the Quality of Observational Cohort and Cross-Sectional Studies

The guidance document below is organized by question number from the tool for quality assessment of observational cohort and cross-sectional studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

Questions 2 and 3. Study population

Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interest at the time they were recruited?

An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994. In this example, the population is clearly described as: (1) who (men over 40 years old with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women ages 34 to 59 years of age in 1980 who were in the nursing profession and had no known coronary disease, stroke, cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards.

In cohort studies, it is crucial that the population at baseline is free of the outcome of interest. For example, the nurses' population above would be an appropriate group in which to study incident coronary disease. This information is usually found either in descriptions of population recruitment, definitions of variables, or inclusion/exclusion criteria.

You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list.

If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.

Question 4. Groups recruited from the same population and uniform eligibility criteria

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

Most cohort studies begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies–which is when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for cardiovascular disease than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic. This study recruits groups from different clinic populations, so this example would get a "no." However, the women nurses described in the question above were selected based on the same inclusion/exclusion criteria, so that example would get a "yes."

Question 5. Sample size justification

Did the authors present their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed.

A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of

effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes."

However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question–i.e., it may have been an exploratory, hypothesis-generating study.

Question 6. Exposure assessed prior to outcome measurement

This question is important because, in order to determine whether an exposure causes an outcome, the exposure must come before the outcome.

For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort (large epidemiological studies like Framingham used this approach). However, for other cohort studies, the cohort is selected based on its exposure status, as in the example above of depressed diabetic men (the exposure being depression). Other examples include a cohort identified by its exposure to fluoridated drinking water and then compared to a cohort living in an area without fluoridated water, or a cohort of military personnel exposed to combat in the Gulf War compared to a cohort of military personnel not deployed in a combat zone.

With either of these types of cohort studies, the cohort is followed forward in time (i.e., prospectively) to assess the outcomes that occurred in the exposed members compared to nonexposed members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly, the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred.

For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and nonexposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome.

Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data), where the exposures and outcomes are measured during the same timeframe. As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Question 6 should be "no."

Question 7. Sufficient timeframe to see an effect

Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? In the examples given above, if clinical depression has a biological effect on increasing risk for CVD, such an effect may take years. In the other example, if higher dietary sodium increases BP, a short timeframe may be sufficient to assess its association with BP, but a longer timeframe would be needed to examine its association with heart attacks.

The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined. Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.

Question 8. Different levels of the exposure of interest

If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed? (for example, for drugs: not on the medication, on a low dose, medium dose, high dose; for dietary sodium, higher than average U.S. consumption, lower than recommended consumption, between the two). Sometimes discrete categories of exposure are not used, but instead exposures are measured as continuous variables (for example, mg/day of dietary sodium or BP values).

In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose-response relationships between exposures and outcomes–e.g., the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose-response relationships lends credibility to the hypothesis of causality between exposure and outcome.

For some exposures, however, this question may not be applicable (e.g., the exposure may be a dichotomous variable like living in a rural setting versus an urban setting, or vaccinated/not vaccinated with a one-time vaccine). If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively towards the quality rating.

Question 9. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable–for example, have they been validated or are they objective? This issue is important as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP, where there may be quite a difference between usual care, where clinicians measure BP however it is done in their practice setting (which can vary considerably), and use of trained BP assessors using standardized equipment (e.g., the same BP device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged). In each of these cases, the former would get a "no" and the latter a "yes."

Here is a final example that illustrates the point about why it is important to assess exposures consistently across all groups: If people with higher BP (exposed cohort) are seen by their providers more frequently than those without elevated BP (nonexposed group), it also increases the chances of detecting and documenting changes in health outcomes, including CVD-related events. Therefore, it may lead to the conclusion that higher BP leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher BP were seen more often; thus, more CVD-related events were detected and documented simply because they had more encounters with the health care system. Thus, it could bias the results and lead to an erroneous conclusion.

Question 10. Repeated exposure assessment

Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified. Also, multiple measurements enable investigators to look at changes in exposure over time, for example, people who ate high dietary sodium throughout the followup period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

Question 11. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable–for example, have they been validated or are they objective? This issue is important because it influences confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups.

An example of an outcome measure that is objective, accurate, and reliable is death–the outcome measured with more accuracy than any other. But even with a measure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (if body weight is the outcome of interest).

Similar to the example in Question 9, results may be biased if one group (e.g., people with high BP) is seen more frequently than another group (people with normal BP) because more frequent encounters with the health care system increases the chances of outcomes being detected and documented.

Question 12. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not involved in the care of the patient and had no information about the study participants' exposure status. The committee would then be provided with copies of participants' medical records, which had been stripped of any potential exposure information or personally identifiable information. The committee would then review the records for prespecified outcomes according to the study protocol. If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 13. Followup rate

Higher overall followup rates are always better than lower followup rates, even though higher rates are expected in shorter studies, whereas lower overall followup rates are often seen in studies of longer duration. Usually, an acceptable overall followup rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90 percent followup, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent followup rate.

Question 14. Statistical analyses

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome–that are not of interest to the research question–should be controlled for in the analyses.

For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

Some general guidance for determining the overall quality rating of observational cohort and cross-sectional studies

The questions on the form are designed to help you focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for cohort studies is the extent to which the results reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study–in other words, the ability of the study to draw associative conclusions about the effects of the exposures being studied on outcomes. Any such flaws can increase the risk of bias.

Critical appraisal involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of poor quality. Low risk of bias translates to a rating of good quality. (Thus, the greater the risk of bias, the lower the quality rating of the study.)

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the exposure and outcome, the higher quality the study. These include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding–all concepts reflected in the tool.

Generally, when you evaluate a study, you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no" you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the

study or doubt the ability of the study to accurately assess an association between exposure and outcome?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and consideration of the concepts for minimizing bias.

Appendix 6. The quality criteria for critical appraisal of observational studies adapted from the CRD handbook

Quality criteria for critical appraisal of observational studies

1. Are the study participants adequately described? For example look for adequate descriptive data on age, sex, baseline health status, and other relevant variables.

2. If there is a comparison or control group, are they similar to the intervention group, in terms of variables that may affect the outcome of the intervention (including demographic and other socio-demographic characteristics). This may be achieved by matching or other means – it may be taken into account in the statistical analysis – for example, by means of ANCOVA or regression techniques.

3. If the study involves an assessment of an intervention, is the intervention clearly described, with details of who exactly received it?

4. If the study is an etiological study (e.g., does maternal stress cause behaviour problems in children?) were the independent and dependent variables adequately measured (that is, was the measurement likely to be valid and reliable)? This may include valid reliable measures, such as well-validated questionnaires if appropriate.

5. Are the measures used in the study the most relevant ones for answering the research question?

6. If the study involves following participants up over time, what proportion of people who were enrolled in the study at the beginning, dropped out? Have these ‘‘drop-outs’’ introduced bias?

7. Is the study long enough, and large enough to allow changes in the outcome of interest to be identified?

8. If two groups are being compared, are the two groups similar, and were they treated similarly within the study? If not, was any attempt made to control for these differences, either statistically, or by matching? Was it successful?

9. Was outcome assessment blind to exposure status? (That is, is it possible that those measuring the outcome introduced bias?)

(Adapted from the CRD handbook)

Source: Mark Petticrew; Helen Roberts. Systematic reviews in the social science: a practical guild; Chapter 5; 136. https://ia801603.us.archive.org/31/items/B-001-002-450/Pettigrew-Roberts-SR-in-the-Soc-Sc.pdf